Remarks

Entry of the foregoing and further and favorable reconsideration of the above-identified application is respectfully requested. By the foregoing amendment, claims 1 and 16 have been amended to recite that the pharmaceutical composition has improved therapeutical indices as compared to the administration of a sodium channel blocker alone. Support for this amendment to claims 1 and 16 may be found, at the very least, on page 4, lines 6-17. Moreover, claims 17 and 24 have been canceled, and claims 18-23 have been amended to be dependent solely on claim 16. Finally, claims 4-7 have been amended to be dependent solely on claim 1, and claims 3 and 19 have been amended to correct an obvious typographical error. The claims have been amended solely to expedite prosecution, and in no way avers to the correctness of any rejection of the claims. Applicants reserve the right to pursue the canceled subject matter in a continuation application. No new matter enters by way of this amendment.

Restriction Requirement

The Examiner continues to maintain the Restriction Requirement first set forth in the Office Action mailed April 21, 2009. Applicants would again like to reiterate their traversal of this requirement, and incorporate herein their arguments provided in their May 21, 2009, Response to Restriction Requirement.

Rejection of Claim 24 Under 35 U.S.C. § 112, First Paragraph

Claim 24 has been rejected under 35 U.S.C. § 112, first paragraph, for purportedly not being enabled by the specification as filed. By the foregoing amendment, claim 24 has been canceled, thereby rendering its rejection moot.

In light of the cancelation of claim 24, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-4, 6, 16, 18-20, 22 and 24 Under 35 U.S.C. § 103(a)

Claims 1-4, 6, 16, 18-20, 22 and 24 have also been rejected under 35 U.S.C. § 103(a) for purportedly being obvious over Fitzgerald et al. (2(3) TECHNIQUES IN

REGIONAL ANESTHESIA AND PAIN MANAGEMENT 119-129 (1998)) in view of Coe et al. (U.S. Appl. Publ. No. 2001/0036943A1) and further in view of Carson et al. (U.S. Patent No. 6,191,142). For at least the reasons set forth below, withdrawal of this rejection is believed to be in order.

Fitzgerald et al. discusses numerous classes of compounds, including antidepressants, anticonvulsants, and antiarrhythmics, that have been studied for their effect on chronic pain. According to Fitzgerald et al. "there is little evidence in the form of trials to support" the use of lamotrigine or fluoxetine for the treatment of chronic pain. (Fitzgerald et al. at 119). Fitzgerald et al. also discusses the pharmacokinetics and side-effects of selective serotonin reuptake inhibitors, such as fluoxetine, and notes that side effects include nausea, diarrhea, headaches, insomnia, etc. (*Id.* at 121-122). Fitzgerald et al. further discusses the pharmacokinetics and side effects of two sodium channel blockers, lamotrigine and phenytoin. (*Id.* at 125-126). Side effects of the administration of lamotrigine and phenytoin include dizziness, diplopia, ataxia and skin rashes. (*Id.*)

Coe et al. discloses a pharmaceutical composition that they purport may be useful for the treatment of acute, chronic and/or neuropathic pain and migraines, wherein the composition comprises a nicotine receptor partial agonist, an analgesic agent and a pharmaceutically acceptable carrier. (Coe et al. at ¶ 0004). Coe et al. provides a long list of possible analgesics that could be used in their disclosed composition, and includes selective serotonin uptake inhibitors in this list. (*Id.* at ¶¶ 0006 and 0138). Also included in the list of possible "analgesics" are tricyclic anti-depressants, anti-histamines, caffeine and steroids. (*Id.* at ¶ 0138). However, Coe et al. provides no data showing that any of their claimed compositions are effective for treating acute, chronic and/or neuropathic pain, let alone data showing that the co-administration of a nicotine receptor partial agonist and a selective serotonin reuptake inhibitor is more effective for treating acute, chronic and/or neuropathic pain than either the administration of nicotine receptor partial agonist or a selective serotonin uptake inhibitor alone. Coe et al. merely discusses biological assays that could be used to determine the compositions effect on pain. (*Id.* at ¶¶ 0285-0297).

Carson et al. teaches compositions for the treatment of neuropathic pain that comprise an aroyl aminoacyl pyrrole. (Carson et al. at col. 2, line 52 – col. 3, line 35).

Carson et al. makes no mention of the use of a selective serotonin uptake inhibitor in a composition for treating neuropathic pain.

None of the references cited by the Examiner disclose or suggest treating chronic pain by administering in combination a sodium channel blocker and a selective serotonin uptake inhibitor. Moreover, in view of the teachings of Fitzgerald et al. that sodium channel blockers, such as lamotrigine and phenytoin, and selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, have little if any effect on chronic pain, one of skill in the art would have had no motivation to prepare a pharmaceutical composition comprising both a sodium channel blocker and a selective serotonin reuptake inhibitor or to use such a composition for the treatment of chronic pain.

In addition, the claims as amended recite that the pharmaceutical composition comprising both a sodium channel blocker and a selective serotonin reuptake inhibitor has improved therapeutical indices when administered to a mammal as compared to the administration of a sodium channel blocker alone. The applicants have shown that the administration of a selective serotonin reuptake inhibitor together with a sodium channel blocker increases the potency of the sodium channel blocker with respect to its reflex inhibitory activity, tremor inhibitory activity and its analgesic effect, but did not greatly affect the side effect profile of the sodium channel blocker (as shown by the rotarod test). (*See* the specification as filed at pages 7-11). Nothing in Fitzgerald et al., Coe et al. or Carson et al. would suggest to one of skill in the art that a composition comprising both a sodium channel blocker and a serotonin reuptake inhibitor would have a more potent therapeutic profile, but would not increase the side effects. Thus, a *prima facie* case of obviousness has not been established.

Even if a *prima facie* case of obviousness had been established by the Examiner, the unexpected results obtained by the applicants would overcome such a finding. The increased therapeutic potency of sodium channel blockers when administered in combination with a serotonin uptake inhibitor, combined with no increase in the severity of side effects, was unexpected and surprising. The data provided in the specification shows:

1) The reflex inhibitory activity of sodium channel blockers is enhanced when the sodium channel blocker is administered in combination with various serotonin

uptake inhibitors. (*See* pages 7-8 and Figures 1-3 of the specification as filed). This was especially surprising as serotonin uptake inhibitors are known to induce movement disorders, including tardive dyskinesia. (*See* Raphael J. Leo, *Movement Disorders Associated With the Serotonin Selective Reuptake Inhibitors*, 57(10) J. CLIN. PSYCHIATRY 449-54, 450 (1996) ("Leo") (attached hereto as Exhibit A)). Thus, one of ordinary skill in the art would not have expected that a serotonin uptake inhibitor would enhance the reflex inhibitory activity of sodium channel blockers.

2) The tremor inhibitory activity of sodium channel blockers is enhanced when the sodium channel blocker is administered in combination with serotonin uptake inhibitors. (*See* pages 8-9 and Figure 4 of the specification as filed). This also was surprising because serotonin uptake inhibitors are known to induce tremors. (*See* Leo at 450). Thus, one of ordinary skill in the art would not have expected that a serotonin uptake inhibitor would enhance the tremor inhibitory activity of sodium channel blockers.

3) The antiepileptic potency of sodium channel blockers is enhanced when the sodium channel blocker is administered in combination with serotonin uptake inhibitors. (*See* pages 10-11 of the specification as filed). This was surprising because the administration of serotonin uptake inhibitors alone were shown to have little or no effect on the inhibition of maximal electroshock seizures. (*Id.* at 10). Thus, one of ordinary skill in the art would not have expected that a serotonin uptake inhibitor would enhance the antiepileptic potency of sodium channel blockers.

4) The analgesic potency of sodium channel blockers is enhanced when the sodium channel blocker is administered in combination with serotonin uptake inhibitors. (*See* page 12 of the specification as filed). This is especially surprising in view of numerous publications (dated before and after the filing date) indicating that sodium channel blockers, such as lamotrigine, and serotonin uptake inhibitors, such as sertraline, have very little effect on chronic pain. *See* M. Titlic et al., *Lamotrigine in the Treatment of Pain Syndromes and Neuropathic Pain*, 109(9) BRATISL. LEK. LISTY. 421-24 (2008) (attached as Exhibit B) (which concludes that lamotrigine has no significant effect on chronic pain); Yee-Chi Lee & Phoon-Ping Chen, *A Review of SSRIs and SNRIs in Neuropathic Pain*, 11(17) EXPERT OPIN. PHARMACOTHER. 2813-25 (2010) (Attached as Exhibit C) (which concludes that "[t]he evidence for efficacy of SSRIs in the treatment of

neuropathic pain is moderate at best." (*Id.* at 2821)); P.J. Wiffen & J. Rees, *Lamotrigine for Acute and Chronic Pain*, COCHRANE DATABASE SYSTEMATIC REVIEWS 2007, Issue 2 Art. No. CD006044 (abstract attached hereto as Exhibit D) (which concludes that "[t]he limited evidence currently available suggests that lamotrigine is unlikely to be of benefit for the treatment of neuropathic pain."); B. Safirstein, et al., *Efficacy of Lamotrigine in Painful Diabetic Neuropathy: Results From Two Large Double-Blind Trials*, 24th ANNU. SCI. MEET. AM. PAIN SOC. (March 30-April 2, Boston) 2005, Abst. 701 (abstract attached hereto as Exhibit E) (which concludes that lamotrigine is effective for relieving neuropathic pain only at high doses (300-400mg/day)); and Aaron I. Vinik et al., *Lamotrigine for Treatment of Pain Associated With Diabetic Neuropathy: Results of Two Randomized, Double-Blind, Placebo-Controlled Studies*, 128 PAIN 169-79 (2007) (attached hereto as Exhibit F) (which concludes that the two double-blind, placebo-controlled studies "did not show consistent efficacy of lamotrigine in the treatment of pain associated with diabetic neuropathy." (*Id.* at 178)).

5) The motor side effects caused by sodium channel blockers were only slightly increased when the sodium channel blockers were administered in combination with serotonin uptake inhibitors. (*See* page 11 of the specification as filed). This was especially surprising since serotonin uptake inhibitors when administered alone showed strong potency in the rotarod test. (*Id.* at Table 3). *See also* Leo, where serotonin uptake inhibitors are shown to induce movement disorders.

Thus, one of ordinary skill in the art would not have expected that serotonin uptake inhibitors would enhance the reflex inhibitory potency, the tremor inhibitory potency, the antiepileptic potency and the analgesic potency of sodium channel blockers, let alone would not cause an increase in the potency of sodium channel blockers on motor side effects. Not only would the teachings of Leo have motivated one of skill in the art not to administer a sodium channel blocker with a serotonin uptake inhibitor (as the known effects of serotonin uptake inhibitors on reflexes and tremors would have discouraged such a combination), one of skill in the art in no way would have expected the highly advantageous results of making such a combination. Because the serotonin uptake inhibitors enhance the reflex inhibitory potency, the tremor inhibitory potency, the antiepileptic potency and the analgesic potency of the sodium channel blockers, without

also enhancing the undesirable motor side effects, the dosage of sodium channel blockers needed to obtain a therapeutic result is reduced, thereby lowering the undesirable side effects. (*See* Vinik at 179, where it is shown that the incidence of adverse events increased as the dosage of lamotrigine was increased from 200 mg to 400 mg).

In fact, studies published since the filing date of the present application indicate that when lamotrigine and sertraline are administered together at low doses (100 mg and 50 mg respectively), each dose ineffective alone for treating chronic pain, the combination provides a good therapeutic effect. *See* Márta Thán et al., *Concerted Action of Antiepileptic and Antidepressant Agents to Depress Spinal Neurotransmission: Possible Use in the Therapy of Spasticity and Chronic Pain*, 50 Neurochem. Intl. 642-52 (2007) (attached hereto as Exhibit G) (which shows that the effectiveness of lamotrigine is significantly enhanced by the pre-treatment with sertraline, and that the combined effect is supra-additive (*Id.* at 649)); and M.J. Molnar & G. Karpati, *Efficacy and Safety of Combination of Lamotrigine and Sertraline in Neuropathic Pain Management*, 64 (6, Suppl. 1) Neurology Abst. P02.159 (2005) (abstract attached hereto as Exhibit H) (co-administration of 100 mg/day of lamotrigine and 50 mg/day of sertraline decreased pain scores by 25.6% in neuropathic pain patients with no severe adverse events.) This supra-additive effect of the combined administration of a sodium channel blocker and a serotonin uptake inhibitor would not have been expected by one of ordinary skill in the art.

In light of these remarks, withdrawal of this rejection under 35 U.S.C. § 103(a) is in order, and the applicants respectfully request the same.

Conclusion

Examination and further and favorable reconsideration of this Application is respectfully requested.

Applicants believe that the present Application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Movement Disorders Associated With the Serotonin Selective Reuptake Inhibitors

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Background: To review the case reports and case series of movement disorders ascribed to the use of serotonin selective reuptake inhibitors (SSRIs).

Method: Reports of SSRI-induced extrapyramidal symptoms (EPS) in the literature were located using a MEDLINE search and review of bibliographies.

Results: Among the 71 cases of SSRI-induced EPS reported in the literature, the most common side effect was akathisia (45.1%), followed by dystonia (28.2%), parkinsonism (14.1%), and tardive dyskinesia-like states (11.3%). Among patients with Parkinson's disease treated with SSRIs, there were 16 cases of worsening parkinsonism. Patients who developed dystonia, parkinsonism, or tardive dyskinesia were older on average than patients with akathisia; 67.6% of affected patients were females. Fluoxetine, the most commonly prescribed SSRI to date, was implicated in 53 (74.6%) of cases of SSRI-induced EPS. Several reports (57.7%) were confounded by the concomitant use of other medications that can contribute to the development of EPS.

Conclusion: SSRI-induced EPS are probably related to agonism of serotonergic input to dopaminergic pathways within the CNS. Several patient-dependent and pharmacokinetic variables may determine the likelihood that EPS will emerge. Although these side effects are infrequent, clinicians should be alert to the possibility of their occurrence.

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With generally fewer side effects than the tricyclics and monoamine oxidase inhibitors, the serotonin selective reuptake inhibitors (SSRIs) have become the most widely prescribed antidepressants in the United States. Owing to the popularity of these agents, increasing attention has been directed at adverse drug events associated with their use, the severity of which had been unappreciated in premarketing clinical trials. For example, a growing body of case reports and reviews on SSRI-induced sexual dysfunction has recently emerged.[1–4] This article addresses a previously underrecognized but clinically significant consequence of SSRI use, namely, the development of movement disorders, i.e., extrapyramidal symptoms (EPS) and tardive dyskinesia. These disorders can be uncomfortable for patients, influence compliance, and contribute to significant psychosocial and occupational impairments.

THE ASSOCIATION OF SSRI USE AND EPS

Medication-induced movement disorders are now included in the appendix of DSM-IV, to be listed, whenever appropriate, on Axis I.[5] These disorders include EPS related to neuroleptic use, i.e., dystonia, akathisia, and parkinsonism. Separate diagnostic criteria are also included for medication-induced tardive dyskinesia and postural tremor. The inclusion of these iatrogenic disorders acknowledges the potential untoward influences of prescribed medications contributing to noncompliance and emphasizes the importance of considering measures to prevent and/or treat such disorders. The addition of the category, Medication-Induced Movement Disorder Not Otherwise Specified, acknowledges that agents other than neuroleptics, e.g., antidepressants, can result in the development of comparable movement disorders.[6–11]

As regards SSRI-induced EPS, product literature provided by Eli Lilly and Company indicates 375 cases of akathisia, 218 cases of dystonia, and 76 cases of tardive dyskinesia associated with fluoxetine use as of December 31, 1995 (data on file, Lilly Research Laboratories, Indianapolis, Ind.). Similarly, the World Health Organization Collaborating Centre for International Drug Monitoring has 438 reports of motoric side effects associated with fluoxetine.[12] The Drug Safety Research Unit in Southampton, United Kingdom, received 35 reports of EPS associated with paroxetine.[13] Because the aforementioned reports largely consist of spontaneously generated, i.e., unsolicited, reports, inferences regarding the prevalence of SSRI-associated motoric side effects cannot be generated from these data. No data are currently available

about individuals who may have experienced comparable side effects but did not report them. It is reasonable to speculate that the symptoms had to be quite severe for patients to report them without solicitation.

This paper presents an analysis of case reports and case series indicating the association of movement disorders and SSRI use. Attempts are made to describe possible mechanisms for the emergence of these disorders and to address the clinical issues of prevention and treatment.

METHOD

Case reports and case series reporting movement disorders and SSRI use were generated by a MEDLINE search and review of bibliographies from each article retrieved. MEDLINE was searched from January 1979 to March 1996, and the terms *extrapyramidal symptoms, dystonia, parkinsonism, drug-induced akathisia,* and *drug-induced dyskinesia* were cross-referenced with each of the following: *antidepressants, serotonin uptake inhibitors, fluoxetine, sertraline, paroxetine,* and *fluvoxamine.* The individual cases were then categorized by type of motoric side effect; categorization was based on the most salient symptoms described in the published report. Case summaries that described torticollis, muscle spasm, opisthotonos, dystonia, blepharospasm, trismus, jaw tightness, or tongue protrusion were categorized as dystonic reactions. Those describing pacing, restlessness, or an inability to remain still were classed as akathisia. Reports categorized as involving parkinsonism described two or more cardinal signs, e.g., cogwheel or lead-pipe rigidity, bradykinesia, resting tremor, masklike facies, gait disturbances, and impaired postural reflexes. Case summaries classified as involving tardive dyskinesia typically reported choreoathetotic movements affecting the face, limbs, or trunk. Documents and articles reporting numbers of cases of motoric side effects associated with the use of an SSRI, but lacking descriptions of motor symptoms or patient data, were not included. In particular, the product information provided by Eli Lilly and the paper by Choo[13] could not be included in the analyses that follow.

RESULTS

Forty-two articles were obtained,[12,14–54] reporting 71 cases of de novo motor symptoms after SSRI use. Akathisia* was reported in 32 cases (45.1%); dystonia† in 20 cases (28.2%); parkinsonism[14–16,18,19,25,32,51] in 10 (14.1%); tardive dyskinesia-like movements[12,22,27,30,34,44,48,54] in 8 (11.3%), and tremors[12,28,42] in 7 (9.9%). Patients could not always be categorized in mutually exclusive groupings, e.g., two patients had both akathisia and dystonia[46,50] and four patients had tremor in addition to another motoric side effect.[12,28,42] Two findings were unexpected. Curiously, one of the cases of dystonia occurred upon abrupt *discontinuation* of fluoxetine.[28] In addition, the fact that only seven cases of tremor were reported is less than would be expected given prior estimates of new-onset tremor arising in 5% to 16% of SSRI-treated patients.[55–57] It is possible that the development of an isolated tremor in SSRI-treated patients is not of clinical significance to warrant publication as a case report or case series.

The mean ± SD age for patients experiencing tardive dyskinesia was 55.4 ± 22.2 years; for patients with parkinsonism, 53.9 ± 18.1 years; for patients with dystonia, 49.7 ± 20.0 years; and for patients with akathisia, 37.8 ± 13.7 years. The patients who had both akathisia and dystonia were not included in this analysis. The four groups differed significantly for age, $F = 3.96$; $df = 3,62$; $p < .01$. Two-way comparisons revealed that patients developing tardive dyskinesia, parkinsonism, or dystonia were significantly older than those developing akathisia.

Of the 71 cases, 23 (32.4%) were males.[12,17,26–29,34,42,43] A binomial test of the hypothesis of a male:female ratio of 50:50 revealed a probability of 0.002 of obtaining 23 or fewer males in a sample of 71 cases. The numbers of males in each of the movement disorder categories were 9/18 (50%) for dystonia; 3/30 (10%) for akathisia; 1/2 for combined dystonia and akathisia; 3/10 (30%) for parkinsonism; and 2/8 (25%) for tardive dyskinesia.

In 53 cases (74.6%), the implicated drug was fluoxetine.‡ More recent reports have emerged demonstrating comparable side effects resulting from sertraline (8 cases, 11.3%)[37,38,40,41,45,46,50]; fluvoxamine (6 cases, 8.5%)[21,32,34,35,49,52]; and paroxetine (4 cases, 5.6%)[47,48,53] use.

The mean dose of fluoxetine employed in those cases (N = 15) resulting in dystonia was 40 mg/day (range, 20–80 mg/day); for akathisia (N = 20), the mean dose was 42 mg/day (range, 5–140 mg/day); for parkinsonism (N = 9), the mean dose was 36.3 mg/day (range, 15–80 mg/day); and for tardive dyskinesia (N = 6), the mean dose was 33 mg/day (range, 20–80 mg/day). In the six cases of sertraline-induced akathisia, the mean dose was 67.9 mg/day (range, 25–200 mg/day); there were two reports of combined dystonia and akathisia (100 mg/day and 200 mg/day, respectively) and no reports of parkinsonism associated with sertraline use. For fluvoxamine, there was one case each of tardive dyskinesia and parkinsonism; the doses were 100 mg/day and 200 mg/day, respectively. The doses of fluvoxamine in the cases resulting in akathisia were 200 mg/day and 300 mg/day, respectively, and for the two cases resulting in dystonia, 100 mg/day and 200

*References 12, 17, 21, 23, 24, 26, 31, 33, 37–39, 47, 52, 53.
†References 12, 20, 28, 29, 35, 36, 42, 43, 48, 49.
‡References 12, 14–31, 33, 36, 39, 42–44, 51, 54.

mg/day, respectively. For paroxetine, there was one case each of dystonia and tardive dyskinesia and two cases of akathisia; the dose in all four cases was 20 mg/day. The interval between treatment initiation or dose change and onset of side effects was variable. For dystonia, the range extended from 3 days[46] to 14 months[43]; for akathisia, 12 hours[17] to 4 months[12]; for parkinsonism, 4 days[14,16] to 1 year[51]; and for tardive dyskinesia-like movements, 3 days[22] to 1 year.[54]

In 41 cases (57.7%), patients had been concurrently treated with other medications. Five (7.0%) patients were treated with lithium,[12,19,22,45] 11 (15.5%) with neuroleptics,* four (5.6%) with carbamazepine,[12,25,33] two (2.8%) with metoclopramide,[12,23] and 19 (26.8%) with miscellaneous medications including benzodiazepines,[17,26,39] buspirone,[12] thyroxine,[12,20,33] or other antidepressants.[12,26,41]

With regard to treatment, anticholinergic agents were employed to reverse SSRI-induced dystonia in five cases,[29,35,36,42,46] but none had been used to treat those cases in which parkinsonism emerged. One patient with parkinsonism responded to low-dose treatment with carbidopa/levodopa.[51] β-Blockers were employed in 10 cases of akathisia[17,24,26,33,37,53]; seven cases were treated with benzodiazepines,[33,38–41,45] two cases were treated with both β-blockers and benzodiazepines,[23,47] and one case was successfully treated with a serotonin antagonist.[52] Eleven patients who developed akathisia experienced an improvement in their symptoms with dose reductions or drug cessation.[21,26,31,33,37,39,50] Complete remission of tardive dyskinesia occurred in three SSRI-treated patients after drug cessation[30,44,54]; however, symptoms persisted in the other five patients despite drug cessation.[12,22,27,34,48]

Seven articles[48,58–63] reported 16 cases of patients with preexisting parkinsonism worsened by the use of SSRIs. Fluoxetine was implicated in 12[58–61] cases; fluvoxamine[63] and paroxetine[48,62] were each implicated in two cases. The mean fluoxetine dose employed in these cases was 16.9 mg/day (range, 20 mg every 4 days to 20 mg/day). The mean fluvoxamine dose employed was 125 mg/day (range, 100–150 mg/day); the paroxetine was administered at 20 mg/day in both cases. Information on patient age and gender, duration of treatment, and coadministered drugs was often omitted for these 16 cases.

DISCUSSION

One of the difficulties encountered in this retrospective review is that the data reflect only published cases or case series. Little is known about others who may have experienced comparable symptoms while treated with SSRIs but whose cases have not been published. There is a lack of well-controlled epidemiologic research focusing on SSRI-induced movement disorders. The precise measures of the prevalence rates of SSRI-induced dyskinesias are lacking at this time, however, the rates are thought to be low.

A retrospective review such as this is limited by a lack of a uniform approach to the assessment and description of movement disorders. Distinguishing movement disorders from other syndromes can be difficult,[53] e.g., differentiating akathisia from agitated affective states or anxiety. Terms such as *restlessness* or *akathisia* may have been used quite variably by different authors.[56] One study of fluoxetine-treated patients revealed that 30% experienced "jitteriness," which encompassed a wide range of reactions including mild anxiety, nervousness, and akathisia.[64] By contrast, some authors made a point of describing the severity of the akathisia, making it clear that they were not merely reporting nervousness.[17,31,33,52] It is possible that, as with akathisia, the terms *dystonia* and *parkinsonism* have been variably applied by different authors. In addition, distinguishing movement disorders from each other can be difficult.[53] For example, akathisia may be difficult to differentiate from tardive dyskinesia. It is possible that tremor might be misperceived as anxiety or akathisia[56] and that this might account for underreporting of this side effect in case studies.

The pathophysiologic mechanisms for drug-induced movement disorders are poorly understood. Blockade of dopamine (D_2) receptors in the basal ganglia and dopaminergic tracts has been implicated in neuroleptic-induced EPS. It seems likely that SSRI-induced EPS result from some interaction between serotonergic and dopaminergic pathways.

There are diffuse interconnections between serotonergic and dopaminergic nuclei.[65,66] The serotonergic input to dopaminergic systems appears to be inhibitory.[67] In rats, fluoxetine was shown to inhibit the synthesis of catecholamines in dopamine-rich areas of the forebrain, hippocampus, and extrapyramidal regions. Neurophysiologic and electric stimulation studies[68] have demonstrated the inhibitory effects of raphe fibers on extrapyramidal neurons and reversal of the inhibition by serotonin antagonists.

The mechanisms underlying SSRI-induced EPS are likely to be more complex than has been suggested by the animal models above. For example, the case of the occurrence of dystonia upon fluoxetine withdrawal[28] is inconsistent with the aforementioned models. Further, serotonin and its agonists have been reported to *improve* symptoms of parkinsonism[69–71] and dystonic symptoms, e.g., blepharospasm.[72] It is possible that serotonergic innervations also influence GABA and cholinergic pathways[65,73] and thereby contribute to the development of EPS. Just how the SSRIs induce EPS in some patients, but improve parkinsonism or dystonia in others, may be clarified by a better understanding of these interconnections.

*References 12, 16, 18, 27, 33, 36, 38, 43, 45.

Hypersensitivity of postsynaptic dopamine receptors has been offered as the underlying mechanism of neuroleptic-induced tardive dyskinesia, whereas tricyclic-induced tardive dyskinesia is thought to involve noradrenergic hypersensitivity and increased anticholinergic activity.[7] The mechanism of SSRI-induced tardive dyskinesia is less clear, as all but three patients who developed it had prior or current neuroleptic exposure.[12,22,27,44]

As with neuroleptic-induced EPS, SSRI-associated movement disorders have a tendency to be elicited idiosyncratically by any of a number of agents of the same class. The majority of cases (74.6%) involved an association between fluoxetine and EPS. Presumably, this dramatic preponderance is attributable to the fact that fluoxetine was the first of the SSRIs and the most often prescribed; however, pharmacologic differences among the SSRIs may be involved. For example, SSRIs with longer half-lives, e.g., fluoxetine, would be expected to exert a more enduring inhibition of central dopaminergic systems. The dosages and duration of treatment were variable, precluding making statements regarding dose relationships. Some cases displayed the rapid onset of symptoms characteristic of neuroleptic-induced EPS.[74] Curiously, in one of the eight cases in which tardive dyskinesia-like movements developed, the latency occurred after 3 days.[22]

Another pharmacologic difference among the SSRIs of potential import on the development of EPS is dopamine reuptake inhibition. Sertraline has been noted to exhibit a direct augmenting effect on dopamine reuptake inhibition[75–77]; inhibitory serotonergic input to dopaminergic systems would be mitigated by such direct augmentation. Paroxetine, fluvoxamine, and fluoxetine have lower potencies than sertraline for dopamine reuptake inhibition in vitro.[77,78] In vitro activity need not necessarily reflect what happens in vivo; nevertheless, these differences in dopamine agonism may contribute to a lesser risk of EPS occurring with sertraline.

In a number of the cases (57.7%), the concomitant use of other medications that can produce EPS, e.g., neuroleptics or metoclopramide, has the potential to confound. It is possible that pharmacokinetic interactions occurred, leading to increased availability of the SSRI, the concurrently administered drug, or both. For example, fluoxetine has been reported to increase serum levels of haloperidol,[79] pimozide,[80] and carbamazepine.[81,82] Such drug combinations might increase the likelihood of EPS.

Alternatively, medications that normally do not produce EPS may, when combined with an SSRI, predispose a patient to EPS. Several commonly prescribed drugs can inhibit the cytochrome P450 enzymes, interfering with SSRI metabolism and thereby increasing SSRI availability.[83] One patient who had taken fluoxetine 60 mg/day uneventfully for 1 year developed parkinsonism after the addition of cimetidine.[51] Several other cases of EPS were also prescribed drugs dependent on the P450 enzyme system for metabolism, e.g., cimetidine,[38] ranitidine.[12,38]

It is possible that some patients are more vulnerable than others to SSRI-induced EPS.[14] Included are (1) elderly patients whose vulnerability may be related to neuronal loss[32,43]; (2) patients in whom circulating levels of an SSRI are particularly high, either because of high doses or reduced hepatic clearance; (3) patients with current or prior neuroleptic exposure[44]; and (4) patients with compromised nigrostriatal functioning.[48,58–63] These determinants need not be mutually exclusive. Thus, advancing age may lead to both neuronal loss and reduced hepatic functioning. Like neuroleptic-induced EPS, parkinsonism tended to occur in older patients. In contrast to neuroleptic-induced dystonia, SSRI-induced dystonia tended to occur in older patients as well. However, because of the limitations cited previously, it is impossible to speculate on the influence of age in the development of these side effects. Further, the rate of spontaneously occurring dyskinesias increases with advancing age. Controlled studies comparing movement disorders among SSRI- and placebo-treated patients are required.

Similarly, one can only speculate on the influence of gender. In the cases reviewed here, females were represented significantly more often than males. While females may be more vulnerable to EPS, there is a potential confound in that the prevalence of depression is greater among females[5] and more females seek treatment for depression than do males.[84] The gender differences observed in the cases reviewed here may simply reflect these epidemiologic differences.

On the other hand, it is possible that males are more susceptible to SSRI-induced EPS than females. Among SSRI-treated patients involved in the New Zealand Intensive Medicines Monitoring Programme, females (N = 3539) exceeded males (N = 1917) by a significant margin.[12] Nevertheless, the number of males who developed movement disorders (N = 8) was approximately equal to the number of females (N = 7) who did so.

Similar to neuroleptic-related disorders, SSRI-induced akathisia and parkinsonism was found by the present review to occur more frequently in females than in males. However, unlike neuroleptic-induced dystonia that affects males more frequently, the number of cases of SSRI-induced dystonia was equal among males and females. Large scale, prospective studies are required to assess the determinants of any gender differences.

Patients with idiopathic Parkinson's disease often suffer from comorbid depression.[85] There is a possibility of exacerbation of parkinsonism with SSRI use. It has been suggested that worsening of parkinsonism by SSRIs is unlikely; otherwise, one would encounter numerous cases in the literature[58,86]; however, patients with Parkinson's disease have often concurrently been treated with antiparkinsonian medications that may have miti-

gated the potential aggravation of parkinsonism by the SSRIs.

Treatments for SSRI-induced movement disorders were comparable with those of neuroleptic-related disorders. Three reports have indicated the efficacy of anticholinergic agents in reversing SSRI-induced dystonia.[36,42,46] It is impossible to make generalizations based on a few case reports, nevertheless, because of the discomfort associated with acute dystonia, a trial of an intramuscular anticholinergic may be considered. Regarding akathisia, β-blockers[17,24,26,37,47,53] and benzodiazepines[40,45,47,64] have been demonstrated to reduce or eliminate the restlessness associated with SSRI use. While dose reduction has been associated with an improvement of symptoms,[21,33,37,39] most patients appear to have done best with drug cessation[12,26,31,33,40,41,50] or use of an alternate antidepressant.[19,31,33,41,50] If parkinsonism develops, the offending agent should be discontinued or the dose lowered. Parkinsonism may emerge only when another agent (an antipsychotic or medication interfering with SSRI metabolism) is introduced[51]; in such cases, symptoms may be ameliorated by merely removing the coadministered drug or by use of an alternate antidepressant. No cases in which anticholinergic supplementation was employed to treat the parkinsonism were found, but this is a possible option. Little can be said about the treatment of SSRI-induced tardive dyskinesia in view of the limited number of cases in which it was reported. In most instances, symptoms did not improve with drug cessation.[12,22,27,34,48] Thus, prevention appears to be of prime importance.

SUMMARY

For most patients, the benefits of SSRI use far outweigh the potential problems of an SSRI-induced movement disorder. Nonetheless, EPS can occur consequent to SSRI use, presumably because of an increase in serotonin's inhibitory influences on dopaminergic pathways. Although this occurs quite infrequently, certain patients appear to be at increased risk, e.g., the elderly, patients with Parkinson's disease, and patients concurrently treated with other medications.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), carbidopa-levodopa (Sinemet), cimetidine (Tagamet), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), metoclopramide (Reglan and others), paroxetine (Paxil), pimozide (Orap), ranitidine (Zantac), sertraline (Zoloft).

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TOPICAL REVIEW

Lamotrigine in the treatment of pain syndromes and neuropathic pain

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Abstract: Anti-epileptic drugs are increasingly used in the treatment of pain syndromes and neuropathic pain. Sodium channel blockers can be effective in the treatment of pain. The object of our interest is the efficiency of lamotrigine in treating the pain. A MEDLINE search was conducted to identify pertinent studies, case reports, letters, and reviews in English published from 1986 to May 2007. The search has indicated efficiency in treating a number of painful syndromes and neuropathic pain; central pain, trigeminal neuralgia and trigeminal neuralgia in multiple sclerosis, pain in multiple sclerosis, SUNCT syndrome, cluster headache, glossopharyngeal neuralgia, neuropathic pain, allodynia, neuralgia after nerve section, postherpetic neuralgia, HIV-associated neuropathy. Further researches are required on the role of lamotrigine in treating the spinal cord injury pain, neuralgia after nerve section, postoperative analgesic requirement, and in migraine *(Tab. 1, Ref. 46).*
Full Text (Free, PDF) *www.bmj.sk.*
Key words: lamotrigine, pain, neuralgia.

Antiepileptic drugs (AEDs) are commonly utilized for non-epileptic condition, including pain syndromes and neuropathic pain. Lamotrigine is a novel antiepileptic agent with at least two antinociceptive properties: it stabilizes the neural membrane through blocking the activation of voltage-sensitive sodium channels, and inhibits the pre-synaptic release of glutamate (1). Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract; it is approximately 55% bound to plasma proteins and has a volume of distribution of about L/kg. The drug is extensively metabolized by conjugation with glucuronic acid. Lamotrigine elimination half-life is 25–30 h (2, 3). The treatment of pain syndromes and neuropathic pain is challenging, in part because of its multiple etiologies. The object of our interest is the efficiency of lamotrigine in the treatment of pain.

Materials and methods

We performed a systematic review of peer-reviewed publication identified through the MEDLINE databases (searched through May 2007). The search term was *lamotrigine, pain, headache,* and the search was limited to clinical trials and articles in English. The search was extended by review of bibliographies from pertinent original reports of data and review articles. Unpublished trials and data presented only in abstracts were not included. The research included 220 references to lamotrigine and its influence to painful syndromes and neuropathic pain.

Review of literature

Central post-stroke pain is usually difficult to treat. Oral lamotrigine 200 mg daily is a well-tolerated and moderately effective treatment for central post-stroke pain and central pain (4–6). Trigeminal neuralgia is a chronic pain syndrome of still unestablished origin. Drug therapy initially helps a great majority of patients. Lamotrigine appears to be the most effective. Meta-analysis suggested; combination carbamazepine with lamotrigine or baclofen is the second-line treatment when monotherapy fails, but the evidence is weak (7–10). Neuropathic pain and paroxysmal symptoms are common in multiple sclerosis (MS) patients, although no double-blind clinical trial has been conducted to support the use of antiepileptic medications in MS (11). Several studies have been recently published addressing the prevalence of pain in MS subjects, finding a frequency of 40 %. The principal neuropathic pain syndromes common in MS are trigeminal neuralgia and dysesthetic pain syndrome. Treatment is based on antiepileptic medications acting on voltage-dependent sodium channels, such as carbamazepine and lamotrigine, or on tricyclic antidepressant (12). Cluster headache is episodic and unilateral, typically surrounds one of eyes, and lasts 15 to 180 minutes; the pain of trigeminal neuralgia lasts just for several seconds and is usually limited to the tissues overlying the maxillary and mandibular divisions of the trigeminal nerve. Cluster headache is

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Tab. 1. Lamotrigine in treatment of painful neuropathy.

Study (author, year)	Neuropathic pain	Conclusion – effect of lamotrigine
Eisenberg et al, 1998	diabetic neuropathy	potentially effective
McCleane, 1999	neuropathic pain	no effect
McCleane, 2000	neuropathic pain	may be effective
Eisenberg et al, 2001	diabetic neuropathy	effective
Vu, 2004	neuropathic pain	first-line or adjunctive therapy
Backonja and Serra, 2004	neuropathic pain	first-line therapy
Singleton et al, 2005	diabetic neuropathy	first-line therapy
Vinik et al, 2007	diabetic neuropathy	effective
Coderre et al, 2007	neuropathic pain	may reduce hyperalgesia
Chong and Hester, 2007	diabetic neuropathy	effective

unique because of its associated autonomic symptoms. The pathophysiology of cluster headache and trigeminal neuralgia are not completely understood. They both appear to have central primary processes, and these findings have prompted investigations of the effectiveness of new antiepileptic drugs for cluster headache prevention and for the treatment of trigeminal neuralgia. The new antepileptic drugs such as lamotrigine are also used in preventing the cluster headache (13). The SUNCT syndrome is characterized by a short-lasting headache in the first division of the trigeminal nerve. It is associated with ipsilateral autonomic symptoms. It is highly refractory to prophylactic medication. Lamotrigine has recently been reported as an effective first-line therapy. It is effective in treating the SUNCT syndrome when used in high doses for a prolonged period of time (14–16). Neuralgia of the glossopharyngeal nerve is a rare disease entity, typically idiopathic, causing paroxysmal and excruciating pain. Lamotrigine is a potentially effective and safe compound in the treatment of painful glossopharyngeal neuralgia (17). Phantom limb pain and stump hypersensitivity post-herpetic neuralgia and causalgia respectively. The new antiepileptics, including lamotrigine, are most useful in the treatment of this type of neuralgia (18). Lamotrigine was well-tolerated and effective in HIV--assocated neuropathic pain in patients receiving neurotoxic antiretroviral therapy (19).Neuropathic pain impacts many people around the world. Patients experience one of many symptoms, such as pain, paresthesia, dysesthesia, hyperalgesia, and allodynia for many years because of unavailable or inadequate treatment. Anticonvulsants, such as lamotrigine, have demonstrated efficacy in relieving the pain associated with diabetic neuropathy in several studies (20–29) (Tab. 1).

Lamotrigine therapy is described in treatment of individuals or smaller groups of subjects (patients) such as the treatment of migraine-related vertigo (30), neuralgia after nerve section (31), spinal cord injury pain (32), postoperative analgesia (33), intractable sciatica (34).

Discussion

Antiepileptic drugs (AEDs) are widely used today to treat epilepsy, migraine, neuropathic pain, and bipolar disorders. Other disorders are also being investigated. The main targets for AEDs in the synapses include the enhancement of GABAergic inhibitory neurotransmission, decrease in glutamatergic excitatory neurotransmission directly or via inhibition of voltage-dependent sodium and calcium channels, and interference with intracellular signalling pathways. Lamotrigine decreases glutamatergic excitability (35). Lamotrigine inhibits excessive neuronal activity; this acute effect appears to be produced by several mechanisms, which fall into three major categories: 1) blockade of voltage-gated sodium channels; 2) indirect or direct enhancement of inhibitory gamma-aminobutyric acid (GABAergic) neurotransmission; or 3) inhibition of excitatory glutamatergic neurotransmission (36). The dose was gradually increased in steps of 25 mg up to the effective dose (mean 250 mg/d). Lamotrigine is effective in trigeminal neuralgia refractory to other treatments, postherpetic neuralgia, painful peripheral neuropathy, HIV neuropathy, diabetic neuropathy, post-stroke pain, and has a significant effect on intractable neuropthic pain, pain related to spinal cord injury, glossopharingeal neuralgia (17, 37–39). Lamotrigine is administered in various head and facial pains such as migraine, cluster headache, neuropathic trigeminal pain, atypical facial pain, and chronic tension-type headache. Lamotrigine was most effective in trigeminal neuralgia and dysesthesia, but had little effect on other head and facial pains (10, 16, 40–42). New AEDs have marked the new era in the treatment of neuropathic pain as the standards of their clinical trials were of higher quality. Lamotrigine is a fourth-line treatment in neuropathic pain, or in adjunctive therapy (43, 44). AEDs are potential alternatives in the treatment of diabetic neuropathy. Lamotrigine was inconsistently effective in pain associated with diabetic neuropathy but was generally safe and well-tolerated (27, 45, 46). All the above facts indicate that lamotrigine therapy is significantly efficient in the treatment of painful syndromes such as trigeminal neuralgia, pain in multiple sclerosis, SUNCT, post-stroke pain, HIV neuropathy, and diabetic neuropathy. Its efficiency when used only as an adjuvant therapy with other painful syndromes involving face and neck is somewhat lower. In cases of glossopharyngeal neuralgia, migraine, sciatic pain, spinal cord injury pain, neuralgia

after nerve section, and postoperative analgesic requirements, only isolated cases are described, wherefore further research is required.

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A review of SSRIs and SNRIs in neuropathic pain

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Importance of the field: Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are becoming increasingly used in the treatment of neuropathic pain and fibromyalgia. However, they are not without adverse effects and their efficacy has not been clear because of conflicting evidence.

Areas covered in this review: We have examined the current evidence on the efficacy of SSRIs and SNRIs in the treatment of neuropathic pain and fibromyalgia. Relevant randomized, placebo-controlled studies were identified through a MEDLINE search of English-language literature from January 1990 to December 2009.

What the reader will gain: The evidence for efficacy of SSRIs in the treatment neuropathic pain is moderate at best. However, SNRIs, venlafaxine and duloxetine have been shown to be effective in the treatment of painful diabetic neuropathy and polyneuropathy. With fibromyalgia, both SSRIs (fluoxetine and paroxetine) and SNRIs (duloxetine and milnacipran) have been shown to improve pain relief, function and quality of life.

Take home message: SSRIs and SNRIs may be considered in the treatment of neuropathic pain if treatment with tricyclic antidepressants and anticonvulsants fails, or if there are contraindications to these drugs. There is also sufficient evidence to indicate that SNRIs are effective in the treatment of fibromyalgia and may be considered early in the treatment of fibromyalgia.

Keywords: fibromyalgia, neuropathic pain, selective serotonin reuptake inhibitor, serotonin noradrenaline reuptake inhibitors, SNRI, SSRI

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1. Introduction

Although antidepressants have been shown to be effective in the treatment of neuropathic pain, not all antidepressants have shown similar efficacy [1,2]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are increasingly used for the treatment of neuropathic pain as they are believed to be better tolerated than traditional tricyclic antidepressants. This review discusses the pharmacology of SSRIs and SNRIs and examines the evidence for their effectiveness in the treatment of different neuropathic pain conditions. Current knowledge of the pain pathways and mechanisms is described to understand the actions of the drugs.

SSRIs selectively block presynaptic neuronal reuptake of serotonin, while SNRIs inhibit both serotonin and noradrenaline reuptake. Although many of these drugs are approved for use in depressive disorders, some – especially SNRIs – may only be approved in specific countries for specific medical indications such as painful diabetic neuropathy and fibromyalgia. Roboxetine, a selective noradrenergic reuptake inhibitor, and bupropion, a second-generation non-tricyclic antidepressant that is

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Article highlights.

- Evidence for efficacy of SSRIs in the treatment neuropathic pain is moderate at best.
- SNRIs (serotonin noradrenaline reuptake inhibitors) are effective in the treatment of painful diabetic and some peripheral neuropathies.
- Tricyclic antidepressants and anticonvulsants should be considered before SSRIs (selective serotonin reuptake inhibitors) and SNRIs in the treatment of neuropathic pain.
- Both SSRIs (fluoxetine and paroxetine) and SNRIs (duloxetine and milnacipran) have shown to improve pain relief, function and quality of life for patients with fibromyalgia and may be used early in treatment in suitable patients.
- SNRIs seem to have better tolerability and fewer adverse effects compared with SSRIs.

This box summarizes key points contained in the article.

also a noradrenaline and dopamine reuptake inhibitor, are not included in this review.

Relevant randomized, placebo-controlled studies were identified through a Medline search of English-language literature from January 1990 to December 2009. Additional references were obtained from a bibliography of relevant published articles. In evaluating the literature and developing recommendations, the Cochrane Database, other systematic reviews and meta-analyses were examined. All randomized, controlled trials (RCTs) were evaluated and the quality rated using the standard Jadad scoring criteria [3].

2. Neuropathic pain mechanisms

Neuropathic pain is defined as '*Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*' [4]. Neuropathic pain is a pathological pain [5]. Unlike nociceptive pain, it does not serve any physiological or protective function. Recent research has led to an understanding that both peripheral and central mechanisms are responsible for the development and maintenance of neuropathic pain. Multiple and diverse mechanisms have been identified, including peripheral sensitization, phenotypic and transcription changes, structural reorganization, central sensitization and decreased descending inhibition [6,7]. These maladaptive events lead to an alteration in the production of neuropeptides, ion channels and receptors, modified threshold and excitability, ectopic and spontaneous discharges, and changes in transmission properties both in the peripheral site of injury and spinal cord, and consequently resulting in hypersensitivity and spontaneous pain. Some of these mechanisms (peripheral and central sensitization) also occur in inflammatory pain, while maladaptive changes such as ectopic excitability, structural reorganization and decreased descending inhibition are unique to neuropathic pain [8].

3. Descending pain modulation

The dorsal horn of the spinal cord receives a network of descending projections from cortex, thalamus and brain stem structure, including hypothalamus, periaqueductal grey, nucleus raphe magus and retroventromedial medulla to modulate the activities in the pain transmission pathway [9-11]. The descending control operates at multiple levels of the pain pathway and is known to exert both inhibitory and facilitatory effects. The inhibitory descending pathways are mediated by 5-hydroxytryptamine (serotonin), noradrenaline, dopamine, GABA and endogenous opiates like endorphin and enkephalin. Under normal conditions, the descending pathway provides a negative feedback control of nociceptive signals at spinal cord level, by attenuating the subsequent signals and prevents excessive pain [11].

Serotonin and noradrenaline are recognized as the main neurotransmitters involved in the modulation of endogenous pain mechanisms via the descending inhibitory pain pathways in both the central nervous system and the spinal cord [9-12]. In experiments with conditional knockout mice that lack central serotonergic neurons, SSRI-mediated analgesia was greatly reduced, suggesting the involvement of serotonergic neurons in the pain pathway [13]. The inhibition of serotonin and noradrenaline reuptake into presynaptic terminals by SSRIs and SNRIs leads to the accumulation of the neurotransmitters at the synaptic junction, and enhances pain suppression via multiple postsynaptic receptor-mediated mechanisms. There is some evidence that analgesic effect induced by antidepressants is mediated significantly through inhibition of noradrenaline rather than serotonergic reuptake [14].

In the events following peripheral nerve injury, excessive nociceptive stimulation and the persistent barrages of impulses from primary afferents to the spinal cord may result in the degeneration and loss of inhibitory neurons in descending pathways leading to enhanced sensitivity and heightened excitability [15-17]. The nociceptive neurons in the dorsal horn may then respond to normally non-noxious primary afferent stimulus, or fire spontaneously even in the absence of persistent noxious stimulus [6,15,18]. In addition, the descending serotonergic facilitatory pathway mediated through 5-HT_3 receptors may also enhance spinal excitability [19,20].

4. Pharmacology of SSRIs and SNRIs

SSRIs block neuronal transport of serotonin leading to increased synaptic serotonin, which in turn stimulates a large number of postsynaptic serotonin (5-HT) receptor types including 5-HT_{1B}, 5-HT_{1D}, 5-HT_3 and 5-HT_{2C}. Stimulation of different receptors leads to analgesia, gastrointestinal side effects and sexual dysfunction (5-HT_3), agitation and restlessness (5-HT_{2C}) [21]. There is also a negative feedback mechanism (by action of 5-HT_{1A} and $_{1D}$) that suppresses serotonin neurons and decreases neuronal release of

serotonin [21]. Some common SSRIs include fluoxetine, paroxetine, citalopram, escitalopram, sertaline and fluvoxamine. Among SSRIs, citalopram is the most selective for serotonin reuptake inhibition compared with noradrenaline reuptake inhibition, while paroxetine is the most potent SSRI [22,23].

SNRIs such as venlafaxine, milnacipran and duloxetine cause a more balanced inhibition of serotonin and noradrenaline reuptake inhibition. Although milnacipran inhibits both serotonergic and noradrenergic reuptake, it has a preference towards noradrenaline reuptake inhibition and also blocks the NMDA receptor [24]. Venlafaxine, on the other hand, is more a serotonin reuptake inhibitor at low dose, and noradrenaline reuptake blockade increases with increasing drug doses [25]. Desvenlafaxine is a new SNRI that has only recently been approved by the FDA for treatment of major depression, while its efficacy for neuropathic pain is unknown [26].

The presynaptic SNRIs' reuptake inhibition of noradrenaline increases the levels of noradrenaline, which in turn couple not only with postsynaptic alpha- and beta-adrenergic receptors but also with the presynaptic alpha-2 receptors. These presynaptic receptors have a pivotal role in antinociception within the central nervous system. Spinal administration of alpha-2 agonists produces potent analgesia in animals and humans [27,28].

Although all of these drugs have no direct postsynaptic effects, fluoxetine [29] and venlafaxine [30] have been shown to block sodium channels. However, unlike tricyclic antidepressants, which are potent voltage-gated sodium channel blockers, with local anaesthetic-like effect [31,32], the clinical significance of this effect in fluoxetine and venlafaxine remains unclear at present.

Most antidepressants are well absorbed after oral administration and have good bioavailability. They are metabolized by cytochrome P450 isoenzymes (CYPs). Individual variation in response of up to 30-fold may occur and is associated with genetic polymorphism of hepatic CYPs [33]. Fluoxetine, sertraline and venlafaxine are metabolized extensively in the liver by the CYP system, including CYP2D6, and are *N*-demethylated to norfluoxetine, norsertraline and desmethylvenlafaxine respectively [33,34]. Most SSRIs have a long half-life, ranging from 18 h (fluvoxamine) to 50 h (fluoxetine) (Table 1) [21]. Some metabolites, such as norfluoxetine, are active inhibitors of serotonin transport with a long elimination half-life of ~ 10 days. Drug interaction is significant with norfluoxetine as it also competes for hepatic CYPs. These effects of norfluoxetine may persist for many days after the cessation of fluoxetine. Although venlafaxine has a short half-life (5 h), slow-release preparation allows less frequent dosing. The elimination half-lifes of SNRIs duloxetine and milnacipran are ~ 12 h [35] and ~ 8 h [36], respectively.

5. Drug interactions

Significant and potentially serious drug interactions may occur with SSRIs and SNRIs as the result of their interaction with other drugs that are also metabolized by CYPs. Many SSRIs and SNRIs inhibit more than one CYP isoenzyme and, therefore, may potentially interact with more than one group of drugs and produce serious adverse effects, especially with drugs of narrow therapeutic index. Significant interactions have occurred between SSRIs and benzodiazepines, β-adrenergic receptor antagonists, theophylline, warfarin, phenytoin, carbamazepine and tricyclic antidepressants [21]. Fluvoxamine, which is known to inhibit CYP1A2, interacts with theophylline and clozapine metabolisms; while fluoxetine, norfluoxetine, sertraline and paroxetine inhibit CYP 2D6 and may increase plasma concentration of tricyclic antidepressants such as nortriptyline. Most of the SSRIs may also inhibit CYP2C and CYP3A4 and interfere with the metabolisms of phenytoin and benzodiazepines, resulting in increased plasma concentrations [37]. Duloxetine inhibits the metabolism of drugs such as desipramine, while its own metabolism is inhibited by paroxetine [38].

With some SSRIs the interactions may last for several days or weeks after cessation of the drug because of their long elimination half-life. It is therefore important to exercise careful patient selection when prescribing SSRIs and SNRIs and monitor their effects, especially in patients with chronic neuropathic pain who may already be on benzodiazepine, other antidepressants, anticonvulsants and medications for common medical conditions including hypertension. Newer generations of SSRIs and SNRIs, such as citalopram, escitalopram, venlaflaxine and milnacipran, are weak or negligible inhibitors of CYP isoenzymes and therefore are less likely to interact with other medications [39].

6. Evidence and clinical efficacy

6.1 SSRIs

6.1.1 Neuropathic pain

Previous studies have reported controversial results on the effectiveness of SSRIs on neuropathic pain. Two early randomized, controlled studies on paroxetine (n = 20) and citalopram (n = 15) in painful diabetic neuropathy showed a significant effect in small-number patient groups [40,41]. In another study (n = 46), fluoxetine was found to improve pain relief in the depressed-patients group, but had no effect overall in patients with painful diabetic neuropathy [42]. However, patient eligibility, selection and randomization were rather complicated in this study. By contrast, fluoxetine used in 98 patients with idiopathic facial pain was found more effective than placebo [43]. A more recent study demonstrated that escitalopram relieved pain in patients with painful polyneuropathy over a 5-week treatment period, but did not improve depression and quality-of-life outcome measures [44]. The authors concluded that only a few patients experienced clinically relevant effects. Similarly, in a randomized, double-blind study comparing desipramine, amitriptyline and fluoxetine in patients with postherpetic neuralgia, clinically meaningful pain relief (moderate or better) was least

Table 1. Elimination half-life.

	$t_{½β}$ (h) ($t_{½β}$ active metabolite)	Common dose range in pain management (mg)
SSRIs		
S-Citalopram	36	20 – 40
Fluoxetine	50 (240)	20 – 40
Flouvoxamine	18	
Paroxetine	22	20 – 40
Sertaline	24 (66)	
SNRIs		
Venlafaxine	5 (11)	75 – 150
Duloxetine	12	60 – 120
Milnacipran	8	100 – 200

SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin noradrenaline reuptake inhibitors.

with fluoxetine (5/15 patients), compared with desipramine (12/15) and amitriptyline (9/17) [45].

Most of the studies on SSRIs have focused on painful diabetic neuropathy. An earlier systemic review reported three studies on SSRIs in patients with painful diabetic polyneuropathy and estimated that the number needed to treat (NNT) was 6.8 [2]. There is limited evidence to indicate that SSRIs may be effective in neuropathic pain conditions at present, and higher quality studies in a larger variety of neuropathic pain conditions are recommended [46]. Current available randomized, placebo-controlled trials are shown in Table 2.

The reason for the lack of effectiveness may be attributed to their mechanism of action. SSRIs are characterized by their ability to inhibit serotonin reuptake without action on noradrenaline reuptake. However, as mentioned, there is some evidence that analgesic effect is mediated through inhibition of noradrenaline rather than serotonergic reuptake [14]. In addition, facilitatory actions of serotonin on $5HT_3$ receptors subserves pronociceptive function and therefore enhances pain [19,20]. Thus, drugs of SSRI profiles will predictably result in less inhibition and therefore weaker effect.

6.1.2 *Fibromyalgia*

The pathophysiological mechanism of fibromyalgia is still not fully understood, although there is increasing evidence that it may be associated with a neuropathic component [47]. Mixed efficacy has been reported with SSRIs in the treatment of patients with fibromyalgia. Several RCTs have examined the role of SSRIs in fibromyalgia with fluoxetine [48-50], citalopram [51,52] and paroxetine [53]. Wolfe [48] found no significant difference between fluoxetine and placebo in a 6-week study. However, this study examined only a modest dose of fluoxetine (20 mg/day). In addition, there was a significant withdrawal rate from the placebo group, mostly due to lack of efficacy. By contrast, in a longer, well-designed trial (12 weeks) using a higher dose of fluoxetine (45 ± 25 mg/day), the SSRI was found to be more effective than placebo in improving, fatigue, depression and pain using the Fibromyalgia Impact (FIQ) and the McGill Pain Questionnaires [50].

Another study found that, although fluoxetine and amitriptyline showed greater effect than placebo, the combination of fluoxetine and amitriptyline was found to have a greater efficacy when given together [49]. The favorable outcome was probably an effect of interaction between the two drugs. The study, however, may be limited by the unblinding when subjects crossed over to the other treatment group. The largest trial for SSRIs with paroxetine controlled-release formulation (n = 116) demonstrated significant improvement in the FIQ scores, including fatigue, anxiety and days felt good, and the Clinical Global Impression – Improvement (CGI-I) score compared with the placebo group [53]. There was a trend favoring pain relief and depression (although not significant).

Two other earlier studies with citalopram found no benefit [51,52], although one of the studies [52] showed improvement in depressive symptoms in the citalopram group. Among the SSRIs citalopram has the most selectivity for serotonin reuptake inhibition, and this may underlie the low efficacy for fibromyalgia. Overall there is some evidence for the effectiveness of fluoxetine and paroxetine in fibromyalgia, although a higher dose of fluoxetine may be required. A recent meta-analysis found that SSRIs improved pain relief, depressed mood and health-related quality of life, but the effect sizes were small and there was no significant effect on fatigue and sleep [54].

6.2 SNRIs

6.2.1 *Neuropathic pain*

There is an increasing number of published trials on SNRIs in neuropathic pain conditions including painful polyneuropathy of diabetic and nondiabetic etiology, postmastectomy pain syndrome, atypical facial pain and fibromyalgia. SNRIs with a better tolerability than SSRIs offer an attractive alternative in the treatment of neuropathic pain.

There is strong evidence for the use of duloxetine in painful diabetic neuropathy from three trials with a total of 1139 patients [55-57]. The efficacy was shown to be sustained over 1 year in an open-label extension of one RCT [55]. In the latter two studies, the duloxetine group demonstrated reduction in the 24-h average pain score as early as 1 week with 60 mg daily or twice daily [56,57]. Health-related outcome measures [56] and Clinical Global Impression-Severity (CGI-S) and CGI-I scores [57] also showed improvement compared with placebo. However, duloxetine has not been studied in other types of neuropathic pain conditions, and therefore its efficacy in these conditions is uncertain.

A dose of 60 mg once daily seems to be as effective as 120 mg daily for pain reduction. The relative risk for > 50% pain reduction at 8 – 12 weeks for painful diabetic neuropathy is 1.63 greater with duloxetine compared with placebo. For a standard dose of 60 mg duloxetine daily, this

Table 2. Randomized, placebo-controlled trials of SSRIs and SNRIs in neuropathic pain.

Pain condition	Study design	Author, year [ref.]	n	Quality	Duration (weeks)	Drug, dose	50% pain relief		Dropout		NNT	Effectiveness & comment
							Active	Placebo	Active	Placebo		
Painful diabetic neuropathy	Cross-over	Sindrup 1990 [40]	20	4	2	Paroxetine 40 mg	10/20	3/20	0/20	0/20	2.9	Paroxetine > placebo Small sample size
Painful diabetic neuropathy	Cross-over	Sindrup 1992 [41]	15	4	3	Citalopram 40 mg	3/15	1/15	2/18	0/18	7.5	Citalopram > placebo NNH = 9 Small sample size
Painful diabetic neuropathy	Cross-over	Max 1992 [42]	46	2	6	Fluoxetine 40 mg	22/46	19/46	3/54	2/54	15.3	Fluoxetine = placebo NNH = 54 Complicated patient selection and randomization
Facial pain	Parallel	Harrison 1997 [43]	98	4	13	Fluoxetine 20 mg	NA	NA	NA	NA	NA	Fluoxetine > placebo Data from abstract only
Polyneuropathy	Cross-over	Otto 2009 [44]	48	5	5	Escitalopram 20 mg	7/41	1/41	5/47	1/47	6.8	Escitalopram > placebo NNH = 11.7 No effect on mood or QOL
Postmastectomy	Cross-over	Tasmuth 2002 [63]	13	4	4	Venlafaxine 18.75 – 75 mg	11/13	NA	1/15	0/13	NA	Venlafaxine > placebo Small sample size Only average pain relief and max. intensity lower, not daily pain intensity
Postmastectomy	Parallel	Reuben 2004 [64]	100	4	2	Venlafaxine 75 mg	NA	NA	0/48	0/47	NA	Venlafaxine > placebo Possible preemptive analgesic effect
Painful diabetic neuropathy	Parallel	Simpson 2001 [60]	11	4	8	Venlafaxine 150 mg	NA	NA	1/6	0/5	NA	Vanlafaxine + gabapentin > gabapentin alone Small sample size Complex randomization NNH = 6
Painful diabetic neuropathy	Parallel	Rowbotham 2004 [61]	244	4	6	Venlafaxine 75 – 225 mg	46/82	27/81	14/163	3/81	4.5.	Venlafaxine > placebo Effect greater with higher dosage (150 – 225 mg) NNH = 20.5
Polyneuropathy	Cross-over	Sindrup 2003 [62]	30	5	4	Venlafaxine 225 mg	8/30	2/29	4/40	2/40	5.2	Venlafaxine > placebo Similar effectiveness as imipramine NNH = 20
Facial pain	Cross-over	Forssell 2004 [66]	30	5	4	Venlafaxine 37.5 – 75 mg	NA	NA	6/30	2/30	NA	Venlafaxine = placebo Higher dosage recommended NNH = 7.5

NA: Not available; NNH: Numbers needed to harm, number of patients to be treated for one dropout due to side effects; NNT: Numbers needed to treat to obtain one patient with > 50% pain relief; QOL: Quality of life as measured by HLQOL measures, e.g., Short-Form Health Survey-36; SNRIs: Serotonin noradrenaline reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors.

Table 2. Randomized, placebo-controlled trials of SSRIs and SNRIs in neuropathic pain (continued).

Pain condition	Study design	Author, year [ref.]	n	Quality	Duration (weeks)	Drug, dose	50% pain relief		Dropout		NNT	Effectiveness & comment
							Active	Placebo	Active	Placebo		
Neuropathic pain conditions	Parallel	Yucel 2005 [67]	60	3	8	Venlafaxine 75 – 150 mg	NA	NA	3/40	1/20	NA	Venlafaxine = placebo Improved quantitative sensory tests NNH = 40
Painful diabetic neuropathy	Parallel	Goldstein 2005 [56]	457	4	12	Duloxetine 20, 60 or 120 mg	158/334	29/101	42/342	6/115	5.3.	Duloxetine > placebo Improved QOL NNH = 14
Painful diabetic neuropathy	Parallel	Raskin 2005 [55]	348	4	12	Duloxetine 60 or 120 mg	101/227	34/113	19/232	3/116	6.9	Duloxetine > placebo NNH = 17.8
Painful diabetic neuropathy	Parallel	Wernicke 2006 [57]	334	5	12	Duloxetine 60 or 120 mg	106/221	29/106	37/226	8/108	4.8	Duloxetine > placebo NNH = 11.1
Fibromyalgia	Parallel	Arnold 2004 [68]	207	5	12	Duloxetine 120 mg	28/101	17/103	18/104	11/103	8.9	Duloxetine > placebo Only effective in female patients Improved QOL NNH = 15
Fibromyalgia	Parallel	Arnold 2005 [69]	354	3	12	Duloxetine 60 & 120 mg	95/230	27/118	52/234	14/120	5.4	Duloxetine > placebo Improved QOL NNH = 9.5
Fibromyalgia	Parallel	Russell 2008 [70]	520	4	24	Duloxetine 20, 60 or 120 mg	134/376	34/144	72/376	19/144	8.3	Duloxetine > placebo Improved QOL NNH = 16.7
Fibromyalgia	Parallel	Gendreau 2005 [72]	125	5	12	Milnacipran 50 – 200 mg	28/97	4/28	17/97	1/28	6.8	Milnacipran > placebo Improved fatigue NNH = 7.1
Fibromyalgia	Parallel	Clauw 2008 [73]	1196	5	15	Milnacipran 100 or 200 mg	NA	NA	172/802	38/405	NA	Milnacipran > placebo Improved QOL and fatigue NNH = 8.3
Fibromyalgia	Parallel	Mease 2009 [74]	888	4	27	Milnacipran 100 or 200 mg	241/665	58/223	163/665	23/223	9.7	Milnacipran > placebo Improved QOL and fatigue NNH = 7
Fibromyalgia	Parallel	Patkar 2007 [53]	116	5	12	Paroxetine 12.5 – 62.5 mg	NA	NA	4/58	1/58	NA	Paroxetine = placebo NNH = 19.3
Fibromyalgia	Parallel	Wolfe 1994 [48]	42	3	6	Fluoxetine 20 mg	NA	NA	1/21	3/21	NA	Fluoxetine = placebo Higher dose recommended NNH = 10.5

NA: Not available; NNH: Numbers needed to harm, number of patients to be treated for one dropout due to side effects; NNT: Numbers needed to treat to obtain one patient with > 50% pain relief; QOL: Quality of life as measured by HLQOL measures, e.g., Short-Form Health Survey-36; SNRIs: Serotonin noradrenaline reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors.

Table 2. Randomized, placebo-controlled trials of SSRIs and SNRIs in neuropathic pain (continued).

Pain condition	Study design	Author, year [ref.]	n	Quality	Duration (weeks)	Drug, dose	50% pain relief		Dropout		NNT	Effectiveness & comment
							Active	Placebo	Active	Placebo		
Fibromyalgia	Cross-over	Golden-berg 1996 [49]	19	5	6	Fluoxetine 20 mg	NA	NA	4/31	1/31	NA	Fluoxetine > placebo Combination with amitriptyline showed greater effect NNH = 10.3
Fibromyalgia	Parallel	Arnold 2002 [50]	60	4	12	Fluoxetine 10 – 80 mg	NA	NA	NA	NA	NA	Fluoxetine > placebo
Fibromyalgia	Parallel	Norregarrd 1995 [51]	42	4	8	Citalopram 20 – 40 mg	NA	NA	NA	NA	NA	Citalopram = placebo
Fibromyalgia	Parallel	Anderberg 2000 [52]	40	4	16	Citalopram 20 – 40 mg	NA	NA	3/21	0/19	NA	Citalopram = placebo NNH = 7

NA: Not available; NNH: Numbers needed to harm, number of patients to be treated for one dropout due to side effects; NNT: Numbers needed to treat to obtain one patient with > 50% pain relief; QOL: Quality of life as measured by HLQOL measures, e.g., Short-Form Health Survey-36; SNRIs: Serotonin noradrenaline reuptake inhibitors; SSRIs: Selective serotonin reuptake inhibitors.

corresponds to an NNT of 6 [58]. There is also significant improvement on quality of life (Short-Form Health Survey-36 [SF-36] and Patient's Global Impression of Change score) with duloxetine at 60 mg or 120 mg daily dosing, but not at a lower dose (20 mg/day). In a separate study comparing duloxetine with routine care, duloxetine 60 mg twice daily showed significant improvement in SF-36 physical component summary score and in the physical functioning, bodily pain, mental health and vitality subscales [59].

Venlafaxine has also demonstrated efficacy in RCTs in patients with neuropathic pain. Two trials (n = 11 and n = 244) showed that venlafaxine relieved painful diabetic neuropathy [60,61], while another trial (n = 40) reported that venlafaxine is as effective as imipramine in relieving pain in nondiabetic polyneuropathy compared with placebo [62]. The study by Simpson [60], however, is not truly an RCT of venlafaxine in the treatment of painful diabetic neuropathy. The study initially randomized 60 patients to either gabapentin or placebo. Eleven patients in the gabapentin group who did not have any improvement were then randomized to either gabapentin with venlafaxine or placebo. An additional phase of the study was uncontrolled, adding venlafaxine to a separate group who failed maximum tolerated gabapentin treatment. Benefits were observed in the gabapentin–venlafaxine group compared with the gabapentin–placebo group.

Pain reduction with venlafaxine was reported to be superior to placebo in two RCTs (n = 13 and n = 100) of postmastectomy pain [63,64]. The study by Tasmuth was limited by the small sample size and, although the average pain relief and maximum intensity during the study were lower, there was no difference in average daily pain intensity [63]. On the other hand, Reuben's study involved a preemptive administration of venlafaxine starting the night before surgery and continued for 2 weeks [64]. He found that venlafaxine reduced the incidence of chest wall, arm and axilla pain in postmastectomy patients and dynamic pain scores were lower in the venlafaxine group at 6 months. There was no difference between venlafaxine and control groups in terms of edema, phantom pain or sensory changes. The NNT for venlafaxine in painful polyneuropathy has been reported to be 3.1 [2].

Venlafaxine is available in both short- and long-acting preparations and generally requires 2 – 4 weeks to titrate to an effective dosage with a weekly increment of 75 mg [65]. It demonstrates best efficacy at higher dosages of 150 – 225 mg daily in various RCTs on painful neuropathy because its balanced inhibition of serotonin and noradrenaline reuptake depends on the drug concentration. With increasing drug doses, noradrenaline reuptake inhibition increases, mainly owing to increasing concentrations of the metabolite O-desmethylvenlafaxine [25]. Two other RCTs in patients with atypical facial pain, various peripheral, central neuropathic pain conditions and postherpetic neuralgia demonstrated inconsistent results [66,67]. The use of lower doses of venlafaxine in one of the studies may have contributed to the inconsistent or negative results.

6.2.2 *Fibromyalgia*

There is consistent evidence for the efficacy of duloxetine to improve pain relief in fibromyalgia from three trials with a total 1072 patients [68-70]. These studies demonstrated significant improvement in FIQ total score and CGI-S and CGI-I scores, as well as the physical and mental components of SF-36 and a reduction in pain severity. The doses of duloxetine 60 mg daily or twice daily were similarly more effective than placebo. It was shown consistently that patients showed improvement regardless of the presence of major depressive disorder, and treatment effect was not dependent on mood improvement. Interestingly, one study found that, although duloxetine-treated female subjects demonstrated significant improvement compared with the placebo group, duloxetine-treated male subjects (n = 12) failed to improve in any efficacy measures [68].

Fatigue is a common symptom reported by patients with fibromyalgia [71]. However, in a meta-analytical review it was found that SNRIs improved pain, sleep, depressed mood and health-related quality-of-life measures, but not fatigue [54]. Like SSRIs, the effect sizes were small. The NNT for a duloxetine dose of 60 mg daily for the treatment of fibromyalgia was 8 (95% CI 5 – 17) [58]. Its efficacy has been shown to be sustained up to 28 weeks in one study [70].

Milnacipran is a second dual noradrenaline and serotonin reuptake inhibitor that has been studied in a large population of patients with fibromyalgia [72-74], but it has not been evaluated in patients with neuropathic pain. A 12-week RCT (n = 125) designed as a dose-finding trial of 25 – 200 mg/day demonstrated that a divided dose (100 mg twice daily) had better analgesic effect and tolerability compared with a 200-mg single, daily dose [72]. It is possible that a single dose may give an inadequate drug concentrations at the end of the day (elimination half-life is ~ 8 h), and this may account for the suboptimal pain relief.

A larger RCT (n = 1196) showed milnacipran in daily doses of 100 mg and 200 mg was significantly more effective than placebo in improvement in pain relief and fatigue. The analgesic response began as early as 1 week after the start of treatment and was sustained throughout the study [73]. Another RCT (n = 888) showed consistent beneficial effect on pain relief within a 27-week study [74]. There were also improvement in patients' global assessment, SF-36 subscales of mental component and fatigue index at a dose of 200 mg daily sustained to 27 weeks. Like duloxetine, pain reduction by milnacipran is seen in both nondepressed and depressed patients; the pain-relieving effects do not occur only through improvement in mood. Both duloxetine and milnacipran have been approved by the FDA for treating fibromyalgia.

7. Adverse effects

All SSRIs and SNRIs have minimal anticholinergic, antihistaminergic and antiadrenergic effects, although paroxetine is noted to have a relatively high anticholinergic potency among

SSRIs. It is therefore not surprising to observe improved tolerability with these drugs compared with tricyclic antidepressants. However, common serotonergic and noradrenergic stimulation including nausea and vomiting, headache, sexual dysfunction, dry mouth, sweating and constipation may still occur. The frequency of side effects seems to be reduced by starting at a lower dose.

7.1 Cardiovascular effects

SSRIs and SNRIs have also been associated with more serious adverse effects. Unlike tricyclic antidepressants, however, SSRIs and SNRIs tend to produce fewer adverse cardiovascular effects [21]. A recent study has shown that SSRIs were associated with increased risk of hip fracture [75], which may be related to drug-induced bradycardia, orthostatic hypotension or syncope [76-78]. Venlafaxine has been associated with dose-dependent hypertension [79], and cardiac conduction abnormalities have been observed in 5% of venlafaxine-treated patients [61]. A retrospective cohort study found that SSRIs in doses of < 100 mg/day (amitriptyline equivalents) did not increase the risk of sudden cardiac death [80], but caution should be exercised in patients with significant cardiovascular disease.

7.2 Hyponatremia

SSRIs and SNRIs have been associated with hyponatremia attributed to syndrome of inappropriate antidiuretic hormone (SIADH) [81-83]. Risk factors include older age, female gender, concomitant use of diuretics and lower baseline serum sodium concentration.

7.3 Suicide

There is a link between antidepressant treatment with suicidal thoughts, with the strongest evidence for SSRI in children and adolescents, while the risk is reduced further at the age of about 30 – 40 years [84]. In a recent report, tricyclic antidepressants were found to have the highest suicide fatal toxicity (deaths in proportion to consumption) and case fatality (ratio of deaths to nonfatal poisoning) rates, followed by SNRIs (venlafaxine), and least with SSRIs (citalopram was worst of this group) [85]. The high suicide fatality with venlafaxine compared with other SSRIs and newer antidepressants is believed to be associated with a high prevalence of adverse drug interactions [86].

7.4 Serotonin syndrome

Serotonin syndrome is a clinical condition that occurs as a result of an iatrogenic drug-induced increase in synaptic serotonin levels [87]. It usually manifests as a triad of neuromuscular hyperactivity, autonomic hyperactivity and altered mental status, and is characterized by clonus, hyper-reflexia, hyperthermia and agitation. While serotonin syndrome may occur in patients taking SSRI or SNRI alone, extra caution should be exercised when the following drugs are prescribed together: tramadol, triptans, monoamine oxidase inhibitors (MAOIs), SSRIs/SNRIs, tricyclic antidepressants, some opioids including pethidine, methadone and propoxyphene, which are weak serotonin reuptake inhibitors [87,88].

7.5 Others

Serious hepatotoxicity has been reported with duloxetine [89]. However, a more recent review concluded that the risk of hepatoxicity was similar to that for other conventional antidepressants, and therefore no routine aminotransferase monitoring was necessary [90].

A recent review of the use of SSRIs and SNRIs during pregnancy found that there was significant association between paroxetine and major malformation. Persistent pulmonary hypertension and self-limiting behavioral syndrome in the neonate with maternal exposure to SSRIs were reported, and therefore SSRIs and SNRIs should be used with caution during pregnancy [91].

8. Tolerance and physical dependence

Therapeutic tolerance tends to occur more often with SSRIs than with older antidepressants [92]. Tolerance to side effects such as nausea develops with continued use of SSRIs. Physical dependence may also occur in patients receiving long-term SSRIs. Patients may complain of malaise, chills, muscle ache, gastrointestinal symptoms, paresthesia, sleep disturbance and irritability when SSRIs are abruptly discontinued. Withdrawal reactions have been reported especially with paroxetine and venlafaxine [93]. It is therefore prudent to discontinue these drugs gradually over a week.

9. Expert opinion

The evidence for efficacy of SSRIs in the treatment of neuropathic pain is moderate at best. In this study we reported five studies on painful diabetic neuropathy [40-42], polyneuropathy [44] and facial pain [43]. Although most showed some positive effects, the benefit is small and of uncertain clinical importance. On the other hand, we found 10 relevant SNRI studies, mainly on painful diabetic neuropathy [55-57,60,61], polyneuropathy [62,67], postmastectomy pain [63,64] and facial pain [66]. These studies, which are more recent and of better quality, suggested that venlafaxine and duloxetine may have a role in neuropathic pain management.

The mechanisms of action of SSRIs and SNRIs on pain transmission and processing have been made clearer by recent advances in pain research, but they are by no means fully elucidated. This has made it difficult to explain their controversial efficacy on neuropathic pain. In this review, we found significant heterogeneity in the studies, and small sample sizes, limited the interpretation of the overall results. Many studies also did not measure functional and health-related quality-of-life outcomes, and therefore compromised the clinical effectiveness of these medications. Most of the patients studied have painful diabetic neuropathy, and it is

uncertain whether the efficacy seen in this condition can be generalized to other neuropathic pain conditions.

Both SSRIs and SNRIs have been widely studied in the treatment of fibromyalgia. We reported six studies on SSRIs [48-53], and six newer studies on SNRIs [68-70,72-74], particularly duloxetine and milnacipran. There is some evidence for the use of fluoxetine and paroxetine in the treatment of fibromyalgia, but the efficacy does not extend to other SSRIs such as citalopram. This brings into question whether the efficacy is, in fact, related to the relative inhibition of serotonin and noradrenaline reuptake, or whether the different outcomes were the result of heterogeneity in study design. On the other hand, strong evidence indicates that duloxetine and milnacipran are effective in improving pain relief, function and quality of life. The pain-relieving effects occur independently of any improvement in mood.

SSRIs and SNRIs have potential side effects and risks of adverse drug interactions. These adverse effects may range from mild (nausea, vomiting, dry mouth) to severe, life-threatening conditions (hepatotoxicity, cardiac arrhythmias). The physician should be familiar with the pharmacology of the drug before prescribing it. With their increased use in neuropathic pain treatment, warning needs to be given that appropriate patient selection is important to avoid unintended complications. SNRIs are more popular because of their better tolerability and fewer adverse effects than SSRIs. The availability of animal models for the studies of neuropathic pain had facilitated a better understanding of pain pathology that predicted SNRIs would be effective. It is therefore not surprising to note that most studies on the use of SSRIs and SNRIs for neuropathic pain and fibromyalgia after 2005 have focused on newer SNRIs such as duloxetine and milnacipran. However, they are expansive and, unless there is definitive evidence, especially for the treatment of neuropathic pain, should not be first-line therapy. It is recommended that tricyclic antidepressants and anticonvulsants should be tried first in the treatment of neuropathic pain before considering SSRIs and SNRIs. However, in the treatment of fibromyalgia, there is already much evidence for SNRIs, and this group of drugs may be considered early in suitable patients.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Lamotrigine for acute and chronic pain.

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Abstract

BACKGROUND: Anticonvulsant medicines have a place in the treatment of neuropathic pain (pain due to nerve damage). This review looks at the evidence for the pain relieving properties of lamotrigine.

OBJECTIVES: To assess the analgesic efficacy and adverse effects of the anticonvulsant lamotrigine for acute and chronic pain.

SEARCH STRATEGY: Randomised Controlled Trials (RCTs) of lamotrigine (and key brand names Lamictal, Lamictin, Neurium) in acute, chronic or cancer pain were identified from MEDLINE (1966 to August 2006), EMBASE 1994 to August 2006 and the CENTRAL register on The Cochrane Library (Issue 3, 2006). Additional reports were sought from the reference list of the retrieved papers.

SELECTION CRITERIA: RCTs investigating the use of lamotrigine (any dose and by any route) for treatment of acute or chronic pain. Assessment of pain intensity or pain relief, or both, using validated scales. Participants were adults aged 18 and over. Only full journal publication articles were included.

DATA COLLECTION AND ANALYSIS: Dichotomous data were used to calculate relative risk with 95% confidence intervals using a fixed effects model unless significant statistical heterogeneity was found. Continuous data was also reported where available. Meta-analysis was undertaken using a fixed effect model unless significant heterogeneity was present (I(2) >50%) in which case a random effects model was used. Numbers-needed-to-treat (NNTs) were calculated as the reciprocal of the absolute risk reduction. For unwanted effects, the NNT becomes the number-needed-to-harm (NNH) and was calculated.

MAIN RESULTS: Sixteen studies were identified. Nine studies were excluded. No studies for acute pain were identified. The seven included studies involved 502 participants, all for neuropathic pain. The studies covered the following conditions: central post stroke pain (1), diabetic neuropathy (1), HIV related neuropathy (2), intractable neuropathic pain (1), spinal cord injury related pain (1) and trigeminal neuralgia (1). The studies included participants in the age range of 26 to 77 years. Only one study for HIV related neuropathy had a statistically significant result for a sub group of patients on anti-retroviral therapy; this result is unlikely to be clinically significant NNT 4.3 (95% CI 2.3 to 37). Approximately 7% of participants taking lamotrigine reported a skin rash.

AUTHORS' CONCLUSIONS: Given the availability of more effective treatments including anticonvulsants and antidepressant medicines, lamotrigine does not have a significant place in therapy at present. The limited evidence currently available suggests that lamotrigine is unlikely to be of benefit for the treatment of neuropathic pain.

PMID: 17443611 [PubMed - indexed for MEDLINE]

Study Name	Lamotrigine in diabetic neuropathy
Design	Pooled/meta-analysis
Conditions	Neuropathy, peripheral; Neuropathy, diabetic
Population	Patients with painful diabetic neuropathy (n=720)
Treatments	Lamotrigine, 200 mg/d x 19 wks Lamotrigine, 300 mg/d x 19 wks Lamotrigine, 400 mg/d x 19 wks Placebo
Biomarker	
Conclusions / Objectives	A significant effect on pain was seen with lamotrigine 400 mg in patients with painful diabetic neuropathy
Notes	A 7-wk dose escalation phase was followed by 12 wks of maintenance treatment
Intervention Type	Drug therapy
Title	Efficacy of lamotrigine in painful diabetic neuropathy: Results from two large double-blind trials
Reference	24th Annu Sci Meet Am Pain Soc (March 30-April 2, Boston) 2005, Abst 701
Authors	Safirstein, B.; et al.
Text	Results from 2 randomized, double-blind, placebo-controlled trials were analyzed to determine the efficacy and tolerability of lamotrigine at doses of 200, 300 and 400 mg in patients with painful diabetic neuropathy. Daily lamotrigine doses were examined in 360 patients in each 19-week study (7 weeks of dose escalation and 12 weeks of fixed dose administration). Mean pain intensity was significantly reduced at week 19 with the 400-mg dose in one study. Pooled analysis was conducted to compensate for a large dropout rate during dose escalation, which was not attributable to adverse events. This showed similar pain intensity reductions with doses of 300 and 400 mg/day, with significantly more patients given 300 mg/day reporting very much or much improvement in overall status compared with placebo.

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Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies

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Abstract

To assess the efficacy and tolerability of lamotrigine in pain associated with diabetic neuropathy, two replicate randomized, double-blind, placebo-controlled studies were conducted. Patients ($n = 360$ per study) with painful diabetic neuropathy were randomized to receive lamotrigine 200, 300, or 400 mg daily or placebo during the 19-week treatment phase, including a 7-week dose-escalation phase and a 12-week, fixed-dose maintenance phase. The mean reduction in pain-intensity score from baseline to week 19 (primary endpoint) was greater ($p \leqslant 0.05$) in patients receiving lamotrigine 400 mg than placebo in Study 2 (observed scores, −2.7 versus −1.6 on a 0- to 10-point scale). This finding was not replicated in Study 1. Lamotrigine 200 and 300 mg did not significantly differ from placebo at week 19 in either study. Lamotrigine 300 and 400 mg were only occasionally more effective than placebo for secondary efficacy endpoints. The 200-mg dose did not separate from placebo. In a *post hoc* analysis of pooled data including only patients who reached their target dose, lamotrigine 400 mg conferred greater ($p \leqslant 0.05$) mean reduction in pain-intensity score from baseline to week 19 than placebo (−2.5 for 300 mg and −2.7 for 400 mg versus −2.0 for placebo). Adverse events were reported in 71–82% of lamotrigine-treated patients compared with 63–70% of placebo-treated patients. The most common adverse events with lamotrigine were headache and rash. Compared with placebo, lamotrigine (300 and 400 mg daily) was inconsistently effective for pain associated with diabetic neuropathy but was generally safe and well tolerated.

Keywords: Lamotrigine; Neuropathic pain; Dibetic neuropathy

1. Introduction

Approximately 25% of patients with diabetes and half of those having diabetes for more than 25 years suffer from diabetic neuropathy, a progressive and heterogeneous condition affecting sensory, motor, and

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autonomic neurons of the peripheral nervous system (Pirart, 1977; Shaw and Zimmet, 1999; Vinik et al., 2003; Duby et al., 2004). Refractory pain in the absence of painful stimuli and/or in response to a normally innocuous stimulus is one of the most significant causes of morbidity in patients with diabetes (Schmader, 2002; Duby et al., 2004; Gooch and Podwall, 2004; Vinik et al., 2005). Painful diabetic neuropathy reduces mobility, diminishes functional ability including the capacity to work and to engage in other normal daily activities, and impairs psychological and social functioning and quality of life (Schmader, 2002; Vinik et al., 2005). The cause of neuropathic pain is unknown but is thought to involve neural hyperexcitability (Pittenger et al., 1999; England and Gould, 2002; Gooch and Podwall, 2004; Vincent and Feldman, 2004; American Diabetes Association, 2005).

Painful diabetic neuropathy is often highly refractory to treatment. Most of the medications tried in painful diabetic neuropathy – non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, selective serotonin reuptake inhibitors, opiates, and anticonvulsants – are moderately effective at best, and many are poorly tolerated (England and Gould, 2002; Duby et al., 2004; Vinik, 2005). Combinations of drugs with the attendant risk of drug interactions are frequently employed in an attempt to improve outcomes. These inadequacies, particularly when considered in the context of the high and growing prevalence of diabetes, which currently affects 18.2 million individuals in the United States (American Diabetes Association, 2005), underscore the palpable need for advances in treatment.

Data from *in vitro* research, animal models, and clinical studies suggest that the anticonvulsant lamotrigine may be useful in the treatment of neuropathic pain (Nakamura-Craig and Follenfant, 1995; Canavero and Bonicalzi, 1997; Lunardi et al., 1997; Zakrzewska et al., 1997; di Vadi and Hamann, 1998; Eisenberg et al., 1998; Klamt, 1998; McCleane, 1998; Carrieri et al., 1999; Devulder and De Laat, 2000; Simpson et al., 2000; Eisenberg et al., 2001; Finnerup et al., 2002; Laughlin et al., 2002; Sandner-Kiesling et al., 2002; Fox et al., 2003; Simpson et al., 2003; Lamictal® Prescribing Information, 2004). Lamotrigine effects dual-action inhibition of neuronal hyperexcitability – the hypothesized basis of neuropathic pain – by blocking voltage-dependent sodium channels and by inhibiting presynaptic release of glutamate, the primary excitatory neurotransmitter (Lamictal® Prescribing Information, 2004). Lamotrigine demonstrates analgesic effects in animal models of neuropathic pain including painful diabetic neuropathy modeled by chronic hyperalgesia in rats with streptozotocin-induced diabetes (Nakamura-Craig and Follenfant, 1995; Klamt, 1998; Laughlin et al., 2002; Fox et al., 2003). Lamotrigine has been reported in clinical studies to be effective in several forms of neuropathic pain including that of diabetic neuropathy, and trigeminal neuralgia (Canavero and Bonicalzi, 1997; Lunardi et al., 1997; Zakrzewska et al., 1997; di Vadi and Hamann, 1998; Eisenberg et al., 1998; McCleane, 1998; Carrieri et al., 1999; Devulder and De Laat, 2000; Simpson et al., 2000; Finnerup et al., 2002; Sandner-Kiesling et al., 2002; Simpson et al., 2003; Grainger et al., 2006). However, in double-blind, placebo-controlled studies, statistical separation of lamotrigine from placebo has not been consistently observed (McCleane, 1999; Silver et al., 2006). The two large, replicate, randomized, double-blind, placebo-controlled studies described herein were undertaken to extend these observations by assessing the efficacy and tolerability of lamotrigine in pain associated with diabetic neuropathy.

2. Methods

2.1. Patients

Male or female outpatients $\geqslant 18$ years of age were eligible for the studies if they had a diagnosis of type 1 or type 2 diabetes mellitus as defined in 2002 by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Expert Committee, 2002); a screening hemoglobin A1c (HbA_{1c}) $\leqslant 11\%$; stable glycemic control (as judged by the investigator) for $\geqslant 3$ months before study entry; diabetic neuropathy defined by bilateral decreased or absent reflexes at the ankles or bilateral decreased vibration, pinprick, fine-touch, or temperature perception in the distal lower extremities at screening; pain associated with diabetic neuropathy for $\geqslant 6$ months but <5 years at screening; and a mean weekly pain score $\geqslant 4$ on an 11-point numerical rating scale completed daily during a 1-week baseline period before randomization. The entry criterion for duration of neuropathic pain ($\geqslant 6$ months but <5 years at screening) was used to exclude patients with pain syndromes other than diabetic neuropathy and those with particularly long-standing refractory pain. Women were eligible only if they had a negative urine pregnancy test at screening and agreed to use acceptable contraceptive methods during the studies or were incapable of bearing children. Exclusion criteria included severe pain not associated with diabetic neuropathy; pain arising from mononeuropathy, osteoarthritis of the ankle or foot, gout, bursitis, or fasciitis; pain attributed to proximal diabetic neuropathy, diabetic mononeuropathy, or diabetic truncal neuropathy; diffuse peripheral neuropathy attributed to causes other than diabetes; multiple sclerosis or other conditions associated with central neuropathic pain; receipt within 30 days before a screening-period baseline visit of nerve blocks or acupuncture for pain relief; and any prior use of lamotrigine. All patients provided written, informed consent.

2.2. Procedures

Two replicate randomized, double-blind, parallel-group, placebo-controlled, multicenter studies (GlaxoSmithKline protocols NPP30004 [Study 1] and NPP30005 [Study 2]) were conducted to evaluate the efficacy and tolerability of lamotrigine for pain associated with diabetic neuropathy. The

protocols for the studies were approved by Institutional Review Boards for each study site, and the studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The studies comprised a 2- to 4-week screening phase, a 1-week baseline phase, and a 19-week treatment phase, which included a 7-week dose-escalation phase and a 12-week, fixed-dose maintenance phase. During the screening and baseline phases, patients were screened for eligibility and were instructed in the use of a diary for recording pain, rescue analgesia use, and sleep interference due to pain each day throughout the studies. Patients who at the end of the baseline phase met eligibility criteria, including at least 4 daily pain observations recorded in the baseline-phase diary and a mean baseline-phase pain score $\geqslant 4$ on an 11-point numerical rating scale, were randomized in a 1:1:1:1 ratio to receive lamotrigine 200, 300, or 400 mg daily or placebo during the treatment phase. Patients were assigned to study treatment in accordance with a computer-generated randomization schedule. A central randomization procedure was used in order to assure that treatment assignment remained balanced. When a patient met the criteria to be included in the study, the study center called into a central system, and that patient received the next treatment assignment as derived from the randomization schedule.

The treatment number was assigned to the patient on the day that the patient was first dispensed study drug. Treatment numbers were assigned in consecutive order starting with the lowest available number. Once a treatment number had been assigned, it was not re-assigned to any other patient at the study center even if a patient withdrew from the study prior to taking any study drug.

The treatment phase began with 7 weeks of dose escalation so that all patients reached their target maintenance dose concurrently and by the beginning of week 8 of treatment (Table 1). For the remaining 12 weeks of the treatment phase (weeks 8–19), the dose of study medication was kept stable at the target dose. Clinic visits occurred on treatment weeks 1, 4, 8, 11, 15, and 19. At the end of the maintenance phase, patients could choose to discontinue lamotrigine or to enter an extension study (GlaxoSmithKline protocol NPP30006) during which they received open-label lamotrigine. Those who chose not to enroll in the open-label extension study had their dose of study medication tapered in a blinded fashion over a period of 1 week.

Table 1
Dose-escalation schedule during weeks 1–8 of treatment

Week	Group (daily dose, mg)		
	Lamotrigine 200 mg	Lamotrigine 300 mg	Lamotrigine 400 mg
1	0	0	25
2	0	25	25
3	25	25	50
4	25	50	50
5	50	50	100
6	50	100	200
7	100	200	300
8	200	300	400

Patients were provided acetaminophen to use during the studies as rescue medication for relief of neuropathic pain. Patients were instructed to take acetaminophen 1000 mg every 4–6 h as needed but to take no more than 4000 mg in 24 h. Non-drug therapies including nerve blocks and acupuncture and any other procedures for pain relief were prohibited for the duration of the studies. Concomitant medications including gabapentin and tricyclic antidepressants were permitted. Analgesics and medications with analgesic properties, such as dextromethorphan, were prohibited.

The protocols for the studies included specific instructions for the management of rash and hypersensitivity reactions because rash, ranging from the simple, morbilliform type to potentially serious rashes, has previously occurred during lamotrigine therapy. Patients developing a rash during treatment with study medication were to be promptly evaluated. If no definite etiology other than study medication could be clearly established, study medication was discontinued immediately.

2.3. Assessments

Efficacy assessments included patient-assessed pain intensity rated daily at bedtime on an 11-point numerical scale (0 = no pain to 10 = worst pain possible) to cover the previous 24 h; sleep interference because of pain rated daily upon awakening on an 11-point numerical scale (0 = pain does not interfere with sleep to 10 = pain completely interferes with sleep); the Short-Form McGill Pain Questionnaire (Melzack, 1987) and the Neuropathy Pain Scale (Galer and Jensen, 1997)completed during clinic visits at the beginning and the dose-escalation phase (week 1), on week 8, and at the end of the maintenance phase (week 19), pain intensity change on the 11-point numerical pain scale (0 = no pain; 10 = worst pain possible) before and after walking a distance of 50 feet in the clinic at the beginning of the dose-escalation phase and at week 8, and rescue medication use recorded daily for the previous 24-h period throughout the dose-escalation and maintenance phases. In addition, physicians and patients completed the Clinician Global Impression of Change scale and the Patient Global Impression of Change scale, respectively, at the beginning of the dose-escalation phase and at week 8. On both scales, change in overall status of the patient was rated on a 7-point scale ranging from *very much improved* to *very much worse*.

The main tolerability assessment was adverse events, defined as any untoward medical occurrences regardless of their suspected cause. Adverse events were recorded throughout the studies including the 1-week taper phase after the end of the treatment period.

2.4. Statistics

Efficacy data were analyzed for all randomized patients who took at least one dose of study medication and provided at least one baseline and one post-baseline efficacy assessment (Intent-to-Treat Population). The primary efficacy endpoint was the change in mean daily pain-intensity score from the baseline week to the last week of treatment (week 19) on the 11-point pain-intensity scale (observed-case analysis). Change in average daily pain score for each patient was computed during the baseline week and week 19 by averaging the daily pain

scores for the 7 days (minimum, 4 days) of those respective weeks. An estimated 56 patients per group were required to provide 90% power to detect a difference of 1.3 points ($SD = 2.1$) between any lamotrigine group and the placebo group using a two-tailed t-test at an alpha of 0.05 for the primary endpoint of mean pain-intensity change score.

Secondary endpoints included mean change from the baseline week to each study week in pain-intensity scores; percentage of patients who were 30% responders and 50% responders, defined as having $\geqslant 30\%$ and $\geqslant 50\%$ reductions, respectively, from baseline in average pain-intensity score at the end of the treatment period; mean change from baseline to week 8 and to the end of the maintenance phase in McGill Pain Questionnaire scores; Neuropathy Pain Scale scores, walking pain-intensity scores, and sleep interference scores; the mean change from baseline to each treatment week in amount of rescue medication used; and the proportions of patients rated as being *much improved* or *very much improved* on the Clinician Global Impression of Change scale and the Patient Global Impression of Change scale.

Change-from-baseline data for all efficacy endpoints were summarized as both observed scores and, for all endpoints except global-impression-of-change results and responder rates, as last-observation-carried-forward (LOCF) scores. In this report, results of analyses of both observed scores and LOCF scores were summarized for the primary endpoint, and observed scores only were summarized for secondary endpoints. Change-from-baseline data were analyzed with analysis of covariance (ANCOVA) methods with the relevant baseline score and concomitant pain medication as covariates. For sleep interference, the ANCOVA included the additional covariate of whether or not a sleep aid was used. Differences between treatments for global impression of change and 30% and 50% responders were analyzed with the Cochrane–Mantel–Haenszel test.

Because multiple treatments were compared with placebo for the primary efficacy endpoint, the overall type I error rate was controlled for by employing sequential testing under the assumption of a monotonic dose–response relationship. The fixed testing sequence involved the comparison of 400 mg versus placebo followed by the comparisons of 300 and 200 mg versus placebo, respectively. The first comparison (400 mg versus placebo) had to meet the statistical significance criterion ($p < 0.05$) before the second comparison was evaluated. Likewise, the second comparison had to meet statistical significance criterion before the third comparison was evaluated. For the secondary endpoints, no adjustments for multiple comparisons were employed.

Tolerability data were analyzed for all patients who took at least one dose of study medication (Safety Population). The primary tolerability measure was the incidence of adverse events regardless of their suspected cause. The incidence of adverse events was summarized for the entire period during which patients received lamotrigine (i.e., the dose-escalation and maintenance phases and the 1-week taper period).

Data from each study were initially analyzed separately as described above. In addition, *post hoc* analyses using LOCF scores were conducted with data from the two studies pooled for the change-from-baseline pain-intensity scores for the subset of patients who reached their target dose of study medication (pooled $n = 151$ for placebo, 149 for lamotrigine 200 mg, 152 for lamotrigine 300 mg, 149 for lamotrigine 400 mg). This *post hoc* analysis of pooled data was undertaken to better understand the effect of treatment in the context of a higher-than-expected dropout rate, particularly prior to reaching the target dose. Pooling of the data was considered justified in view of the similarities between the studies, which had identical designs and methods, were conducted at similar clinical settings in the United States, and were conducted during the same time period. Exclusion of patients who did not reach the target dose was not considered to have biased the tolerability data given that adverse events were an infrequent reason for discontinuation during escalation. (Adverse events were a reason for withdrawal in 8–12% of patients across treatment groups [Table 2]).

3. Results

3.1. Patients

Fig. 1 shows patient disposition for each study. Across treatment groups and studies, approximately 20–30% of patients prematurely withdrew before reaching the target dose of study medication (Fig. 1). Adverse events were the most common reason for premature withdrawal during the dose-escalation phase (Fig. 1).

Table 2 shows the population characteristics of each study. There were 720 subjects randomized (90 per treatment group in two studies). The Safety Population comprised 706 patients, and the Intent-to-Treat population comprised 679 patients. Some of the patients randomized to treatment (14 in Study 1 and 10 in Study 2) were not included in the Intent-to-Treat Population or in efficacy analyses because of substantial study conduct deviations that resulted in the termination of two centers from the studies. Demographics and baseline clinical characteristics of the Safety Population were comparable among treatment groups and between Study 1 and Study 2 (Table 2).

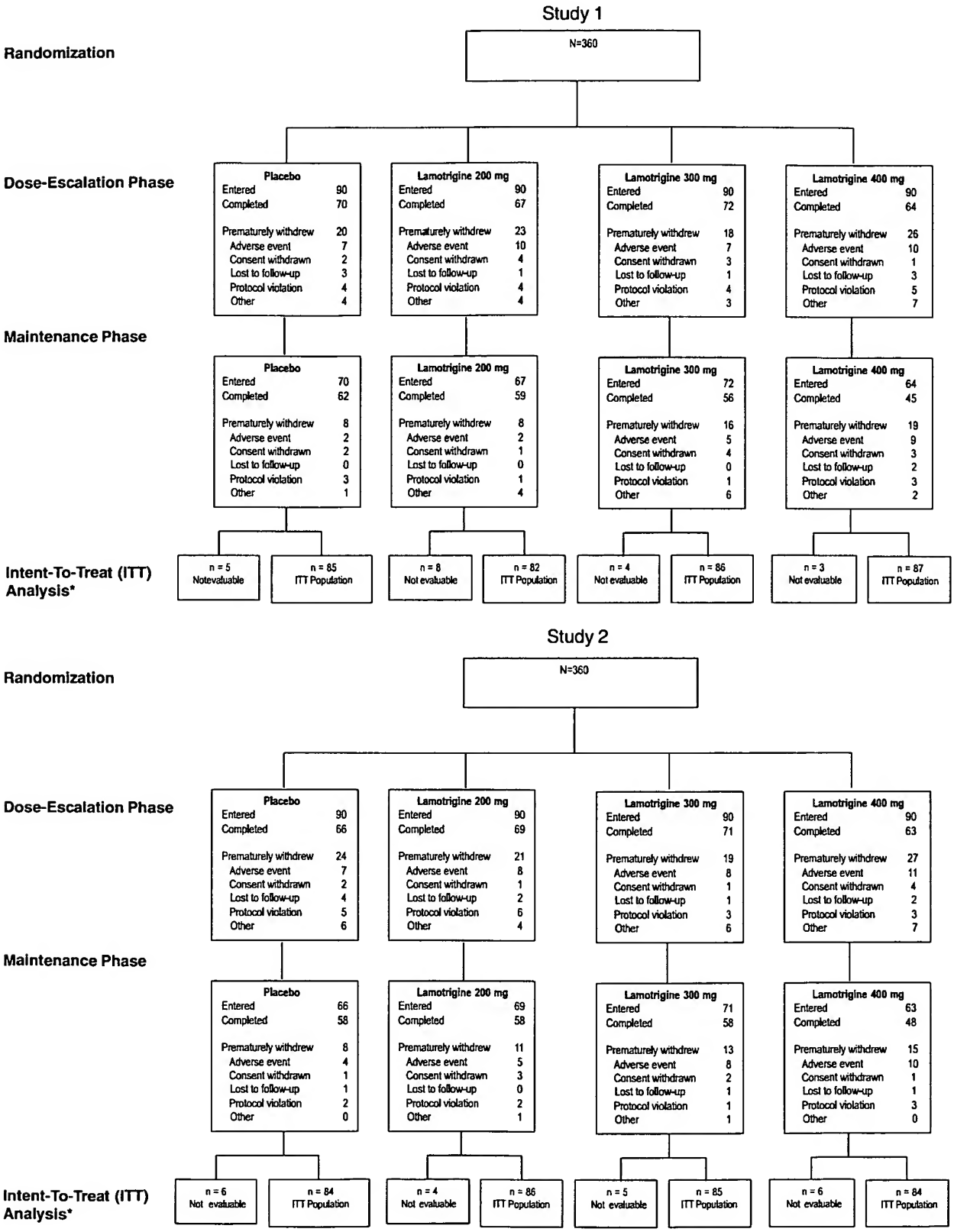
3.2. Efficacy

3.2.1. Pain intensity

Mean pain-intensity scores during the baseline week were comparable among groups and between studies (Table 2). The time course for pain-intensity scores in both studies is depicted in Fig. 2. The mean reduction in pain-intensity score from baseline to week 19 (primary endpoint) was significantly greater ($p \leqslant 0.05$) in patients receiving lamotrigine 400 mg/day than placebo in Study 2 (observed scores, −2.7 versus −1.6). This finding was not replicated in Study 1. Lamotrigine 400 mg was significantly ($p \leqslant 0.05$) more effective than placebo at reducing pain on several treatment weeks before week 19 in both studies (Fig. 2). In the LOCF analyses of mean changes in pain-intensity score from baseline to week 19, statistically significant differences between lamotrigine and placebo were not observed in Study 1 or Study 2.

Table 2
Analysis populations, demographics, and baseline clinical characteristics

	Placebo	Lamotrigine 200 mg	Lamotrigine 300 mg	Lamotrigine 400 mg
Analysis populations				
Study 1				
Number randomized	90	90	90	90
Safety Population, *n* (%)	88 (98)	88 (98)	90 (100)	89 (99)
Intent-to-Treat Population, *n (%)	85 (94)	82 (91)	86 (96)	87 (97)
Study 2				
Number randomized	90	90	90	90
Safety Population, *n* (%)	86 (96)	89 (99)	89 (99)	87 (97)
Intent-to-Treat Population, *n (%)	84 (93)	86 (96)	85 (94)	84 (93)
Demographics and baseline clinical characteristics of safety population				
Mean age, years (SD)				
Study 1	59.8 (10.3)	60.3 (9.8)	60.0 (12.5)	59.6 (10.4)
Study 2	61.6 (11.3)	60.8 (11.2)	59.7 (12.2)	59.0 (12.6)
% male				
Study 1	66	50	50	51
Study 2	56	57	46	54
Ethnicity, *n* (%)				
Study 1				
White	72 (82)	75 (85)	69 (77)	70 (79)
Black	9 (10)	7 (8)	7 (8)	9 (10)
Hispanic	6 (7)	4 (5)	10 (11)	7 (8)
Other	1 (1)	2 (2)	4 (4)	3 (3)
Study 2				
White	75 (87)	81 (91)	77 (87)	72 (83)
Black	6 (7)	5 (6)	7 (8)	11 (13)
Hispanic	3 (3)	3 (3)	2 (2)	3 (3)
Other	2 (2)	0 (0)	3 (3)	1 (1)
Diabetes type, *n* (%)				
Study 1				
Type 1	4 (5)	6 (7)	7 (8)	5 (6)
Type 2	84 (95)	82 (93)	83 (92)	84 (94)
Study 2				
Type 1	8 (9)	6 (7)	9 (10)	6 (7)
Type 2	78 (91)	83 (93)	80 (90)	81 (93)
Mean duration of diabetes, months (SD)				
Study 1	102.3 (88.2)	136.6 (118.2)	126.0 (112.5)	131.7 (125.3)
Study 2	122.2 (110.7)	124.1 (133.5)	110.5 (95.3)	108.2 (85.9)
Mean duration of neuropathic pain, months (SD)				
Study 1	30.6 (16.4)	33.5 (14.7)	29.9 (15.2)	32.2 (16.6)
Study 2	36.6 (16.9)	35.4 (17.8)	33.3 (15.3)	32.4 (15.1)
Mean baseline pain-intensity scores				
Study 1	6.3 (1.5)	6.6 (1.4)	6.0 (1. 5)	6.2 (1.4)
Study 2	6.1 (1.7)	6.0 (1.5)	6.3 (1. 6)	6.5 (1.5)
Concomitant gabapentin or tricyclic antidepressants				
Study 1, *n*				
Gabapentin only	26	23	21	21
Tricyclic antidepressants only	6	3	5	3
Gabapentin + tricyclic antidepressant	3	1	0	1
Study 2, *n*				
Gabapentin only	21	19	17	19
Tricyclic antidepressants only	4	7	8	4
Gabapentin + tricyclic antidepressant	0	2	1	1



*Some of the patients randomized to treatment (14 in Study 1 and 10 in Study 2) were not included in the ITT Population or in efficacy analyses because of substantial study conduct deviations that resulted in the termination of two centers from the studies. These patients are included in the category of "protocol violations"in the figure.

Fig. 1. Patient disposition.

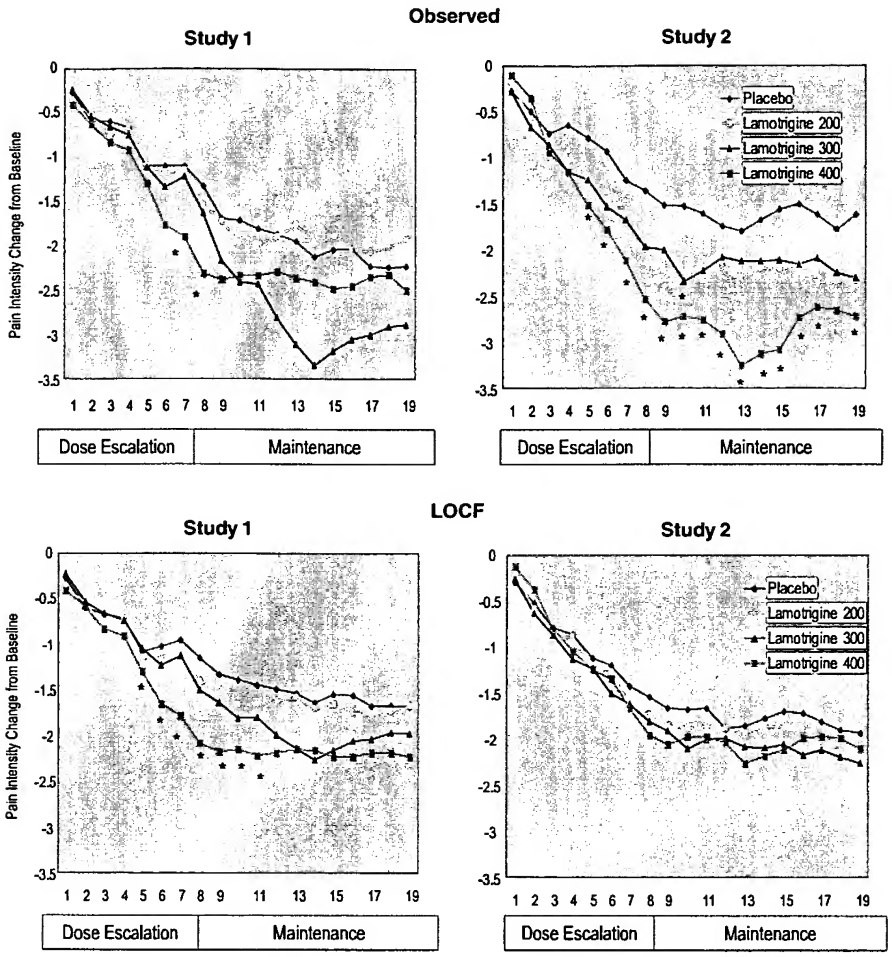


Fig. 2. Adjusted mean change from baseline in pain-intensity scores (observed data and LOCF data) in Studies 1 and 2. $^{*}p < 0.05$ versus placebo.

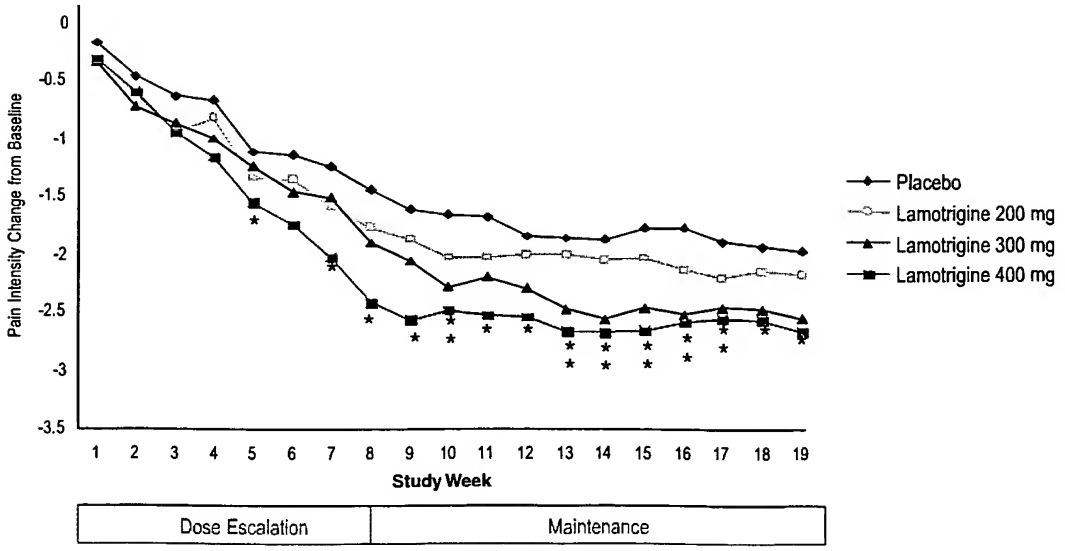


Fig. 3. Adjusted mean change from baseline in pain-intensity scores (patients who reached target dose, *post hoc* LOCF analysis) from pooled studies. $^{*}p < 0.05$ versus placebo.

In the *post hoc* analysis of pooled LOCF data from the subset of patients who reached their target dose (pooled $n = 151$ for placebo, 149 for lamotrigine 200 mg, 152 for lamotrigine 300 mg, 149 for lamotrigine 400 mg), lamotrigine 400 mg, but not 200 or 300 mg, conferred significantly greater ($p \leqslant 0.05$) mean reduction in pain-intensity score from baseline to week 19 than placebo (−2.5 for 300 mg and −2.7 for 400 mg versus −2.0 for placebo, $p \leqslant 0.05$) (Fig. 3). Lamotrigine 300 and 400 mg were consistently more effective ($p \leqslant 0.05$) than placebo at reducing pain throughout much of the maintenance period. The 200-mg dose did not differ in efficacy from placebo at any time point.

3.3. Other efficacy assessments

Differences between lamotrigine and placebo in changes from baseline on secondary efficacy assessments (observed scores) were only occasionally statistically significant; however, the numerical differences consistently favored lamotrigine, particularly with the Neuropathy Pain Scale and the Walking-Pain Intensity Scores (Table 3). Responder rates did not significantly differ between lamotrigine and placebo at the end of treatment in either study ($\geqslant 30\%$ reduction in average pain-intensity score: 38% placebo, 30% 200 mg, 43% 300 mg, 29% 400 mg in Study 1 and 30% placebo, 37% 200 mg, 33% 300 mg, 32% 400 mg in Study 2; $\geqslant 50\%$ reduction in average pain-intensity score 27% placebo, 23% 200 mg, 33% 300 mg, 18% 400 mg in Study 1 and 23% placebo, 24% 200 mg, 24% 300 mg, 24% 400 mg in Study 2).

4. Tolerability

The percentage of patients in whom at least one adverse event was reported was slightly higher in the lamotrigine groups than the placebo group in both studies (Table 4). The incidence of adverse events leading to premature withdrawal from the studies was comparable between the 200- and 300-mg doses of lamotrigine and placebo but was slightly elevated with lamotrigine 400 mg compared with placebo (Table 4). No specific adverse event or group of adverse events accounted for the slightly higher incidence of premature withdrawal in the 400-mg groups.

The most common adverse events reported more frequently among patients in any lamotrigine group than in the placebo group were headache and rash (Table 4). All of the incidents of rash except one were considered to be non-serious. One serious adverse event of rash was reported in a patient in the lamotrigine 200-mg group. This patient was hospitalized for a viral syndrome with rash and fever after receiving lamotrigine 25 mg/day for 10 days during the dose-escalation phase. The rash was reported as a drug-related adverse

Table 3
Summary of results of secondary efficacy assessments (observed scores)

	Timing of efficacy assessment	
	End of dose-escalation phase (week 8)	End of treatment (week 19)
McGill Pain Questionnaire		
Study 1	ns	ns
Study 2	ns	ns
Neuropathy Pain Scale		
Study 1	√ for 300 mg, 400 mg	√ for 300 mg
Study 2	√ for 300 mg	ns
Walking pain-intensity score		
Study 1	√ for 300 mg, 400 mg	ns
Study 2	√ for 400 mg	√ for 400 mg
Sleep interference score		
Study 1	ns	ns
Study 2	√ for 400 mg	ns
Patient Global Impression of Change		
Study 1	ns	√ for 300 mg
Study 2	√ for 300 mg, 400 mg	ns
Clinician Global Impression of Change		
Study 1	√ for 400 mg	ns
Study 2	ns	ns
Rescue medication use[a]		
Study 1	ns	ns
Study 2	ns	ns

ns, non-significant versus placebo; √, $p \leqslant 0.05$ versus placebo.
[a] Rescue medication use generally did not statistically significantly differ between lamotrigine and placebo.

Table 4
Summary of adverse-event data, reported as number (percentage) of patients

	Placebo	Lamotrigine 200 mg	Lamotrigine 300 mg	Lamotrigine 400 mg
Study 1				
n	88	88	90	89
Any adverse event	62 (70)	65 (74)	74 (82)	67 (75)
Any adverse event leading to premature withdrawal from study	5 (6)	10 (11)	10 (11)	15 (17)
Most common adverse events[a]				
Headache	3 (3)	7 (8)	19 (21)	14 (16)
Rash (serious or non-serious)	8 (9)	13 (15)	7 (8)	11 (12)
Nausea	4 (5)	10 (11)	4 (4)	9 (10)
Dizziness	2 (2)	3 (3)	8 (9)	10 (11)
Study 2				
n	86	89	89	87
Any adverse event	54 (63)	63 (71)	65 (73)	64 (74)
Any adverse event leading to premature withdrawal from study	9 (10)	10 (11)	9 (10)	15 (17)
Most common adverse events[a]				
Headache	6 (7)	14 (16)	15 (17)	18 (21)
Rash (serious or non-serious)	8 (9)	9 (10)	10 (11)	14 (16)
Nausea	7 (8)	11 (12)	5 (6)	5 (6)
Dizziness	6 (7)	4 (4)	6 (7)	9 (10)
Arthralgia	8 (9)	9 (10)	3 (3)	2 (2)

[a] Adverse events (regardless of their suspected cause) are listed if they were reported more often in any lamotrigine group than in the placebo group and were reported in >8% of patients in any treatment group.

event. The incident was classified as a serious adverse event because the subject was hospitalized. The rash was judged to be of mild severity and resolved without complications.

Two deaths occurred during the studies. One death, occurring in a 74-year-old placebo-treated patient, was associated with congestive heart failure. The second death, occurring in a 53-year-old patient in the lamotrigine 300-mg group, was thought possibly to be related to a complication of hypoglycemia.

5. Discussion

These two randomized, double-blind, placebo-controlled studies show mixed results with respect to the efficacy of lamotrigine in the treatment of pain associated with diabetic neuropathy. Lamotrigine 400 mg (but not other doses) statistically differed from placebo on the primary endpoint in only one of the two studies. Lamotrigine did not differ from placebo in either study for this endpoint with LOCF analyses. In the *post hoc* analysis of data of patients who reached their target dose in the two studies pooled, statistically significantly ($p \leqslant 0.05$) greater reduction in pain was observed with lamotrigine 400 mg versus placebo for LOCF scores. The 300- and 400-mg doses of lamotrigine were only occasionally statistically significantly more effective than placebo for secondary efficacy endpoints. *Post hoc* analyses (not described in the Results) did not help to explain the lack of separation of lamotrigine from placebo. For example, results for the primary endpoint did not vary as a function of whether or not concomitant gabapentin or tricyclic antidepressants were taken during the study period.

Approximately 20–30% of patients across treatment groups and studies prematurely withdrew before reaching the target dose of study medication. Insofar as suboptimal efficacy or tolerability were causes for premature withdrawal, the high dropout rate probably influenced the results. The high dropout rate might have contributed to the inconsistencies between results of efficacy analyses involving LOCF scores (results from all randomized patients) and those involving observed scores (results from patients who remained in the studies). The relatively high incidence of early premature withdrawal may have resulted in an underestimation of treatment efficacy in LOCF analyses as these analyses carried forward scores of these patients who were likely not to have been on an effective dose of study medication before they withdrew. This possibility is supported by the finding of greater separation of the active treatment groups from placebo in the LOCF analysis of data from the subset of patients who reached their target dose of study medication.

The results of these studies extend previous observations with lamotrigine (di Vadi and Hamann, 1998; Eisenberg et al., 1998; McCleane, 1998; Carrieri et al., 1999; Devulder and De Laat, 2000; Simpson et al., 2000; Eisenberg et al., 2001; Finnerup et al., 2002; Sandner-Kiesling et al., 2002; Simpson et al., 2003). Lamotrigine has been reported effective in the treatment of neuropathic pain (including trigeminal neuralgia, diabetic neuropathy, and HIV-associated distal sensory polyneuropathy) in case reports and open-label studies

(Canavero and Bonicalzi, 1997; Lunardi et al., 1997; di Vadi and Hamann, 1998; Eisenberg et al., 1998; McCleane, 1998; Carrieri et al., 1999; Devulder and De Laat, 2000; Sandner-Kiesling et al., 2002). However, results of double-blind, placebo-controlled studies have been inconsistent (Zakrzewska et al., 1997; McCleane, 1999; Eisenberg et al., 2001; Simpson et al., 2003; Silver et al., 2006). In one of the most recently conducted double-blind, placebo-controlled studies, lamotrigine 200–400 mg daily added to gabapentin, a tricyclic antidepressant, or a non-narcotic analgesic in patients ($n = 107$) with inadequate relief on these medications was not statistically more effective than placebo ($n = 106$) for the primary endpoint of change in pain-intensity score or for secondary efficacy endpoints (Silver et al., 2006). Considering the body of evidence to date on lamotrigine in neuropathic pain, GlaxoSmithKline (manufacturer of lamotrigine) has suspended further development and study of lamotrigine for this use. The results are consistent with the possibility that sodium channel blockade, a mechanism of lamotrigine, is not in itself sufficient to relieve neuropathic pain.

A large placebo response, particularly evident during the latter weeks of treatment, was observed in both the study of lamotrigine adjunctive therapy (Silver et al., 2006) and in the current studies. In the current studies, the large placebo response in the context of the minimum average pain score for enrollment (4 on 0–10 scale) may have contributed to a floor effect that limited drug-associated improvement. During the latter weeks of treatment in these studies – which were of much longer duration than many previous placebo-controlled neuropathy studies typically lasting 5–8 weeks (Backonja et al., 1998; Eisenberg et al., 2001; Richter et al., 2003; Lesser et al., 2004) – the magnitude of the placebo response continued to increase. A large placebo response during the latter weeks of a prolonged treatment period was also observed in a recently reported series of studies ($n = 1269$) with topiramate for painful neuropathy (Topiramate Diabetic Neuropathic Pain Study Group, 2004). After 18–22 weeks of double-blind treatment, reductions in pain scores were numerically, but not statistically significantly, larger with topiramate than with placebo in three double-blind trials.

Lamotrigine was generally well tolerated with a high frequency of adverse events during 19 weeks of treatment in the current studies. The most common adverse events with lamotrigine were headache, rash (all but one incident of which was considered to be non-serious), and dizziness. The tolerability profile of lamotrigine in the current studies is consistent with that observed in other studies of lamotrigine in neuropathic pain as well as in studies of lamotrigine for epilepsy and bipolar disorder (Messenheimer et al., 1998; Matsuo, 1999; Bowden et al., 2004). The incidence of rash (non-serious and serious) in these studies was comparable to or lower than that observed in epilepsy and bipolar-disorder studies (Messenheimer et al., 1998; Bowden et al., 2004); however, the sample size of the current study was too small to assess accurately the potential for serious rash.

In summary, results of two randomized, double-blind, placebo-controlled studies did not show consistent efficacy of lamotrigine in the treatment of pain associated with diabetic neuropathy. Lamotrigine was generally well tolerated in these studies.

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Concerted action of antiepileptic and antidepressant agents to depress spinal neurotransmission: Possible use in the therapy of spasticity and chronic pain

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Abstract

Chronic pain states and epilepsies are common therapeutic targets of voltage-gated sodium channel blockers. Inhibition of sodium channels results in central muscle relaxant activity as well. Selective serotonin reuptake inhibitors are also applied in the treatment of pain syndromes. Here, we investigate the pharmacodynamic interaction between these two types of drugs on spinal neurotransmission *in vitro* and *in vivo*. Furthermore, the ability of serotonin reuptake inhibitors to modulate the anticonvulsant and windup inhibitory actions and motor side effect of the sodium channel blocker lamotrigine was investigated. In the hemisected spinal cord model, we found that serotonin reuptake inhibitors increased the reflex inhibitory action of sodium channel blockers. The interaction was clearly more than additive. The potentiation was prevented by blocking 5-HT_2 receptors and PKC, and mimicked by activation of these targets by selective pharmacological tools, suggesting the involvement of 5-HT_2 receptors and PKC in the modulation of sodium channel function. The increase of sodium current blocking potency of lamotrigine by PKC activation was also demonstrated at cellular level, using the whole-cell patch clamp method. Similar synergism was found *in vivo*, in spinal reflex, windup, and maximal electroshock seizure models, but not in the rotarod test, which indicate enhanced muscle relaxant, anticonvulsant and analgesic activities with improved side effect profile. Our findings are in agreement with clinical observations suggesting that sodium channel blocking drugs, such as lamotrigine, can be advantageously combined with selective serotonin reuptake inhibitors in some therapeutic fields, and may help to understand the molecular mechanisms underlying the interaction.

Keywords: Sodium channels; Serotonin reuptake inhibitors; Spinal reflexes; Spasticity; Chronic pain; Pharmacodynamic interaction

1. Introduction

Voltage-gated sodium channels (VGSCs) are essential for normal cardiac, muscular, and neural functions. Inactivation of VGSCs plays a crucial role in regulation of electrical activity of excitable cells. Different types of inactivation exist, including fast, slow and ultra-slow, and each of these can be modulated by cellular factors or accessory subunits (Goldin, 2003). Abnormally increased activity of VGSCs in the central nervous system (CNS) may lead to pathological states, such as epileptic disorders, chronic pain, or neurodegeneration caused by brain ischemia or chronic neurological diseases. Common therapeutic targets of VGSC blockers among CNS diseases include epilepsies, neurodegenerative diseases and bipolar disorder. Several blockers, such as lidocaine, carbamazepine, and lamotrigine are used for the clinical treatment of chronic pain syndromes (Baker and Wood, 2001; Clare et al., 2000; Lai et al., 2003), as well. Furthermore, recent experimental models of muscle spasticity (Bennett et al., 2004; Li and Bennett, 2003) indicate abnormal functioning of VGSCs in the spinal cord. Accordingly, inhibition of VGSCs has been shown to result in central muscle relaxant activity (Kocsis et al., 2005; Pratzel et al., 1996; Stamenova et al., 2005). Recently, besides the traditionally used tricyclic antidepressants (TCAs), such as amitriptyline, selective serotonin reuptake inhibitors (SSRIs) and mixed monoamine uptake inhibitors are also used as

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first-line treatment for managing pain syndromes (Mattia and Coluzzi, 2003; Mochizucki, 2004; Rowbotham et al., 2004; Stahl et al., 2005; Watson, 1994). A state-dependent, lidocaine-like VGSC blocking action, namely preferential blockade of inactivated sodium channels of overactive neurons involved in pathological processes, has been implicated in their analgesic activity (Hahn et al., 1999; Song et al., 2000; Wang et al., 2004).

VGSCs are subject to modulation by G protein-coupled receptor signaling cascades involving PKA and PKC mediated phosphorylation. Phosphorylation of the sodium channel protein by PKC facilitates slow inactivation (Cantrell and Catterall, 2001; Carr et al., 2003; Chahine et al., 2005; Chen et al., 2006). Phosphorylation of an identified serine residue of the intracellular loop between DIII and DIV by PKC is responsible for the altered inactivation characteristics of the channel. Activation of 5-HT_{2C} receptors in prefrontal cortex neurons results in a negative shift in the voltage-dependence of fast inactivation accompanied with a reduction of the peak current due to a PKC mediated phosphorylation process (Carr et al., 2002). D_1 receptor stimulation also results in phosphorylation of VGSC's serine residues at the cytoplasmic linkers between DI and DII (S554 and S573) and DIII and DIV (S1506) by PKC. Concurrent phosphorylation by PKA seems necessary for a maximal current reduction (Cantrell et al., 2002).

These mechanisms can be activated by various neurotransmitters, like serotonin, dopamine, or acetylcholine (Cantrell and Catterall, 2001). Since SSRIs increase the extracellular concentration of serotonin, it is logical to suppose that besides their direct, lidocaine-like channel blocking action (Hahn et al., 1999; Lenkey et al., 2006) they also modulate sodium channels *via* this indirect way. We hypothesize that a double action on VGSCs, a direct channel blocking action and an indirect one mediated by increased serotonin tone accounts for the analgesic effect of SSRIs.

In order to prove this double action, we performed experiments to study the pharmacological interaction between SSRIs and sodium channel blocking agents. Since spinal sodium channels are involved in the development of both chronic pain states (Millan, 1999) and spasticity disorders (Bennett et al., 2004; Kocsis et al., 2005), we examined the interaction of VGSC blockers and SSRIs at the level of spinal segmental neurotransmission in the rat hemisected spinal cord model, *in vitro*. The reflex inhibitory action of VGSC blockers was markedly enhanced when SSRI compounds were co-applied, and serotonin receptors and PKC were involved in this interaction. To analyze further the underlying molecular mechanisms, namely the possible role of PKC, we also studied the above interaction on cells of spinal neuronal cultures using whole-cell patch clamp recordings. To test if the above synergism also exists under *in vivo* conditions, we also studied spinal reflexes in spinalized rats, anticonvulsant effect in the maximal electroshock seizure; MES (Swinyard et al., 1952) assay, and analgesic effect in the windup model of chronic pain (Herrero et al., 2000; Kovacs et al., 2004), in spinalized rats.

2. Experimental procedures

2.1. Animals

NMRI mice were obtained from Harlan Winkelmann, Borchen, Germany, Wistar and Sprague–Dawley rats from Horst, The Netherlands, and from Toxicoop, Budapest. All experiments were approved by the institutional Ethical Committee and were carried out according to the recommendations of the Hungarian Animal Protection Act (1998), which are in agreement with the guidelines of the corresponding European Communities Council Directive (86/609/EEC). Care was taken to prevent animals from unnecessary suffering.

2.2. Materials

Lamotrigine, eperisone HCl, tolperisone HCl, crobenetine, sertraline, fluoxetine and paroxetine were synthesized at Gedeon Richter Ltd. (Budapest, Hungary). Lidocaine was obtained from EGIS Pharmaceuticals (Budapest). Carbamazepine, riluzole, ketanserin, phorbol-myristil-acetate (PMA), forskolin, mesulergine and 1-(3-chlorophenyl)piperazine (mCPP) were purchased from Sigma–Aldrich Ltd. (Budapest). Citalopram and chelerythrine was purchased from Tocris Bioscience (Ellisville, MO).

For intravenous infusion Rindex solution (containing in mM: NaCl 68, KCl 3.5, $CaCl_2$ 1.25, $MgCl_2$ 0.5, glucose 555) was obtained from Human Ltd. (Budapest). The anesthetic solution for *in vivo* studies contained 0.25% α-chloralose and 10% urethane (both from Sigma–Aldrich) dissolved in distilled water. The cannula for blood pressure monitoring was filled with physiological saline containing 200 IU/ml heparin (Richter). All other drugs, salts and chemicals were purchased from Sigma–Aldrich.

2.3. In vitro spinal reflexes

Experiments were performed according to Otsuka and Konishi (1974) modified by Kocsis et al. (2003). Six-days-old male Wistar rats weighing 13–16 g were used. Rat pups were anesthetized with ether and placed onto crushed ice until their respiration stopped. The spinal cord was removed and hemisected along the midline. Hemicords were transferred into a storage chamber, and were incubated at room temperature (23–26 °C) in standard artificial cerebro-spinal fluid (ACSF; composition in mM: NaCl 124, KCl 3.5, NaH_2PO_4 1.23, $CaCl_2$ 2, $MgCl_2$ 2, $NaHCO_3$ 26, glucose 10) bubbled with carbogen (95% O_2 and 5% CO_2) for at least half an hour. Then, one of the hemicords was placed into a recording chamber and perfused with ACSF at 26 °C.

The L5 dorsal root was stimulated with supra-maximal square-wave current pulses (0.2 mA; 0.1 ms; frequency: 2/min). Glass suction electrodes were used for both stimulation and recording. The first 180 ms of the ventral root reflex (VRR) from the L5 ventral root was recorded.

A computerized data acquisition system was used both for on-line and off-line analyses. Signals were amplified and filtered (bandwidth: 0.02–5000 Hz). Different components of the ventral root reflex responses were separated according to their post-stimulus latencies and durations (Kocsis et al., 2003). Two responses were averaged, stored and subjected to quantitative evaluation. Drugs were added to the ACSF in a cumulative-manner. A new drug, or a higher concentration was only applied when the effect of the former drug application fully saturated. IC_{50} values (*i.e.* the concentration causing 50% inhibition) were calculated by the aid of the curve-analysis function of Origin 6.0 (OriginLab Corp., Northampton, MA), using sigmoid fitting according to the Hill equation.

2.4. In vivo spinal reflexes

Experiments were performed according to Farkas and Ono (1995). Male Wistar rats weighing 280–300 g were anesthetized with a mixture of chloralose (25 mg/kg) and urethane (1 g/kg), i.p. A tracheal cannula was inserted and the animals were artificially ventilated throughout the experiment. Blood pressure was monitored *via* a cannula placed into a carotid artery. The left femoral vein was also cannulated to allow intravenous injections. The spinal cord was transected at the C1 level. Animals were fixed in a spinal stereotaxic frame and a dorsal laminectomy was performed on vertebrae L1–L6. Dorsal and

ventral roots below L3 were cut bilaterally. A pool was formed from the skin of the back and filled with warm paraffin oil. Rectal and oil pool temperatures were maintained at 36 ± 0.2 °C using a heating lamp. Drugs were administered *via* the femoral vein. Throughout the experiments, physiological saline (Rindex) was infused (10–20 ml/kg/h).

The right L5 dorsal root was stimulated with supra-maximal square-wave current pulses (5 V; 0.1 ms; 10/min). Bipolar silver wire electrodes were used both for stimulation and for recording. The first 10 ms of the ventral root reflex (VRR) from the ipsilateral L5 ventral root was recorded. To obtain monophasic potentials, the L5 ventral root was crushed between the two poles of the recording electrode.

Responses were amplified and band-pass filtered (0.5 Hz–5 kHz). Signals were digitized at a sampling rate of 10 kHz. Components of the responses were separated according their post-stimulus latencies and durations and each component was integrated individually. Custom-made computer program controlled both stimulation and data acquisition and performed an on-line data analysis as well.

2.5. Windup

Inflammatory, post-injury and chronic pain states are usually accompanied by increased excitability of certain dorsal horn neurons of the spinal cord. Windup is a short-term increase in the excitability of these neurons during low frequency, high intensity electrical stimulation of the afferent fibres (for a review, see Herrero et al., 2000).

Experiments were performed according to Kovacs et al. (2004). Sprague–Dawley rats (200–300 g) were anesthetized with urethane (1.3–1.8 mg/kg, i.p.). A lack of foot withdrawal to painful stimulation indicated adequate level of anesthesia. The trachea, the femoral vein and one carotid artery were cannulated and the body was mounted in a spinal stereotaxic frame. Animals were spinalized at C1 level, immobilized using D-tubocurarine (1 mg/kg i.v.) and artificially ventilated. Intravenous infusion containing saline, glucose, and D-tubocurarine (1 mg/kg/h) was administered throughout the experiment. The right sciatic nerve was dissected free for a length of 1–2 cm and was placed on a bipolar silver stimulating electrode. A laminectomy was performed from L3–L6, the dura mater was opened and the exposed tissue was covered with warm 0.1% agar–agar gel dissolved in physiological NaCl solution.

Neuronal responses were collected using parylene coated tungsten microelectrodes (impedance 1.5–3 MΩ at 1 kHz), lowered into the spinal cord, using a manual hydraulic microdrive. The responses were amplified, band pass filtered and fed into a window discriminator and an oscilloscope. Collection of neuronal activity as well as controlling the stimulus delivery were performed by a PC equipped with a multifunction instrument control and data acquisition board (PCI-MIO-16, National Instruments, Austin, TX), programmed in LabView 3.1 (National Instruments). Responses of single neurons at the level of L5–L6 segments were recorded from the intermediate and deep layers of the dorsal horn extracellularly. A neuron was included in the study if it responded to pinch (anatomical forceps), to light touch as well as to electrical stimulation (2 ms wide square waves pulses with varying intensity) of the sciatic nerve. Test stimuli were applied to the sciatic nerve and the thresholds for C-fibre responses were determined. The sciatic nerve was stimulated at 10-min intervals using square-wave current pulses at an intensity of 3× C-fibre response threshold. In order to induce windup we applied a train of 16 pulses, delivered at 1 Hz. Firing between 90 and 300 ms after stimulus, defined as C-fibre evoked neuronal responses (Budai, 1994), was evaluated. Windup was calculated as the total number of C-fibre mediated action potentials for all 16 shocks minus 16× the input response (Svendsen et al., 1997). The input was defined as the spike count evoked by the first shock of the corresponding train in the same time window.

2.6. Maximal electroshock seizure test (MES)

Experiments were performed according to Swinyard et al. (1952). Groups of 10 male NMRI mice (20–30 g) were used. Constant current stimuli (20 mA square-wave pulses, 50 Hz for 0.2 s) were delivered through corneal electrodes. Under these conditions all vehicle treated mice showed characteristic hindlimb extension (tonic convulsion) following a short period of clonic convulsions. Lack of the tonic convulsion was regarded as protection and dose–response curves were constructed from the percent of animals protected at each dose.

2.7. Rotarod test in mice

Performance of mice in the rotarod test (Dunham and Miya, 1957) was investigated in order to see whether CNS related motor side effects are potentiated by the combination. NMRI mice weighing 19–22 g were used. The ability of the animals to remain on the rotating rod for 2 min was tested. Groups of 10 mice were treated intraperitoneally with different doses of the test substances. ED_{50} values (*i.e.* the dose causing failure in 50% of the animals) were calculated using probit analysis.

2.8. Whole-cell current measurements

Primary cultures of spinal cord neurons were prepared from 17-day-old Wistar rat embryos. Spinal cords were taken out, washed with Ca^{2+}- and Mg^{2+}-free Hank's balanced salt solution (HBSS) and incubated in HBSS containing 1× Trypsin-EDTA solution for 10 min at 37 °C. The tissue then was placed into Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 6 g/l glucose, 500 μM ketamine, 20 ng/ml nerve growth factor, 1× RPMI 1640 vitamins solution and antibiotics (100 IU/ml penicillin, 0.1 mg/ml streptomycin, 0.25 μg/ml amphotericin B). After trituration, the cell suspension was filtered through a 70 μm mesh, centrifuged twice at 125 × *g* for 10 min and the pellet was resuspended in the medium. Cells were plated at a density of 1.5×10^5 cells/cm^2 on sterilized glass coverslips previously coated with poly-D-lysine. Cultures were kept at 37 °C in a 5% CO_2 atmosphere, one-half of the medium was changed to fresh serum-free medium twice a week.

Inward currents were recorded by the conventional whole-cell patch clamp technique 6–13 days after plating. Coverslips with the attached neurons were transferred to a recording chamber and constantly superfused with the extracellular solution (e.s.) at room temperature. The e.s. used in the sodium current experiments contained (in mM): NaCl 140, KCl 5, $CaCl_2$ 2, $MgCl_2$ 2, HEPES 5, HEPES-Na 5, glucose 20; pH 7.35; 310 mOsm. Patch electrodes (resistances: 2.5–5 MΩ) pulled from borosilicate capillary glass were filled with the intracellular solution: CsF 130, NaCl 15, tetraethylammonium chloride 10, $CaCl_2$ 0.1, $MgCl_2$ 2, ATP-Na_2 2, HEPES 10, EGTA 1; pH 7.25; 290 mOsm.

Sodium currents were evoked by 8-ms-long rectangular step depolarizations to 0 mV from different holding potentials (indicated in Section 3) at 10-s intervals. An Axopatch 200B amplifier and the pClamp 9.2 software package (Axon Instruments, Union City, CA) were used for recording and analysis. Series resistance and capacitive transients were compensated. Test compounds, dissolved in e.s. (dimethyl sulfoxide: 0.1%), were applied onto the cell *via* multi-barrelled pressure-driven pipettes controlled by electromagnetic valves.

Percentage inhibition was calculated from the sodium current peaks in the presence and absence of the test compounds. Inhibition data, presented as means ± S.E.M., were plotted against lamotrigine concentrations. To determine the concentration causing half-maximal inhibition (IC_{50}) data were fitted to the Hill equation. The availability curves of sodium channels were fitted according to the Boltzmann function: $I_{Na} = I_{Na,max}/\{1 + \exp([V_H - V_{H1/2}]/k_H)\}$, where I_{Na} is the peak current amplitude, $I_{Na,max}$ the maximal sodium current (the upper asymptote of the fitted sigmoid curve), V_H the applied holding potential, $V_{H1/2}$ the membrane potential for half-maximal availability, while k_H is the slope factor or width.

3. Results

3.1. SSRIs potentiate spinal reflex inhibitory action of VGSC blockers, in vitro

A typical ventral root reflex potential evoked by dorsal root stimulation in the hemisected spinal cord preparation, consisted of a biphasic monosynaptic action potential (monosynaptic reflex component, MSR) followed by a long-lasting, gradually decreasing depolarisation (compound excitatory postsynaptic potential, EPSP). The peak of MSR followed the stimulus artifact with a latency of about 5 ms. Effect of drugs on the peak-to-peak amplitude of MSR was evaluated.

Table 1
Potentiating effect of selective serotonin reuptake inhibitors (SSRIs) on the reflex inhibitory action of various voltage-gated sodium channel (VGSC) blockers

	IC_{50} value for inhibition of MSR (μM)					
	Alone	In the presence of				
		Fluoxetine (1 μM)	Paroxetine (10 nM)	Sertraline (0.1 μM)	Sertraline (0.5 μM)	Citalopram (5 nM)
Tolperisone	52.4	20.3	14.6	N.T.	N.T.	N.T.
Eperisone	55.7	11.8	N.T.	N.T.	N.T.	N.T.
Lamotrigine	195.9	32.8	52.2	55.7	28.9	43.7
Carbamazepine	212.1	88.2	N.T.	N.T.	N.T.	N.T.
Crobenetine	7.95	2.54	1.59	N.T.	1.29	1.78
Riluzole	30.9	6.30	N.T.	N.T.	N.T.	N.T.
SSRI alone inhibition% (*n*)		2.6% (27)	9.4% (14)	9.3% (9)	25.9% (13)	21.9% (9)

Application of SSRI was started 40–60 min before that of VGSC blockers. The last line of the table shows the percentage effect of SSRI pre-treatment on the reflex responses. SSRIs caused little or moderate inhibition of the reflex and these inhibited responses served as control for the dose–response curves of VGSC blockers. N.T., not tested.

Both VGSC blockers (tolperisone, eperisone, lamotrigine, crobenetine, carbamazepine, riluzole) and SSRI compounds (fluoxetine, paroxetine, sertraline, citalopram) depressed MSR concentration-dependently causing nearly complete, or complete inhibition of the response at sufficiently high concentration. The effect of VGSC blockers was also analyzed in the presence of low concentrations of SSRIs that caused little or moderate inhibition of the reflex, and these inhibited responses served as control for the dose–response curves of VGSC blockers. We found that SSRIs increased the effectiveness of the VGSC blockers in all tested combinations (Table 1). The most pronounced potentiation was obtained when lamotrigine was combined with sertraline; the IC_{50} of lamotrigine decreased about seven-fold in the presence of 0.5 μM sertraline. The IC_{50} value of sertraline on its own to inhibit MSR was 1.5 μM. To see if the synergistic interaction between sertraline and lamotrigine was supra-additive, *i.e.* more than additive summation of the effects occurred, an isobolographic analysis (Kaminski et al., 2001) was performed. The dose–response curves of lamotrigine were determined in the absence or presence of sertraline (0.1 and 0.5 μM; Fig. 1). The isobologram of the reflex inhibitory action of lamotrigine and sertraline, and their combinations shows a clearly supra-additive interaction between the two drugs (Fig. 2). The statistical comparison (chi-square test) of the IC_{50} values of the combinations calculated from the isobologram and those actually determined in the experiments shows a highly significant difference ($p < 0.001$).

Ketanserin, an antagonist of 5-HT_2 receptors, prevented the ability of sertraline to potentiate the reflex inhibitory effect of lamotrigine. In the combined presence of ketanserin (1 μM) and sertraline (0.5 μM), the IC_{50} value of lamotrigine was 250.4 μM, *i.e.* 10 times higher than when co-applied only with sertraline. Ketanserin not only reversed the potentiating action of sertraline, but also decreased the effectiveness of lamotrigine itself. The IC_{50} of lamotrigine to inhibit spinal reflexes increased from 195.9 to 356.6 μM, suggesting that the action of the VGSC blocker is dependent on a tonic serotonergic activation. Mesulergine (1 μM), another blocker of 5-HT_2

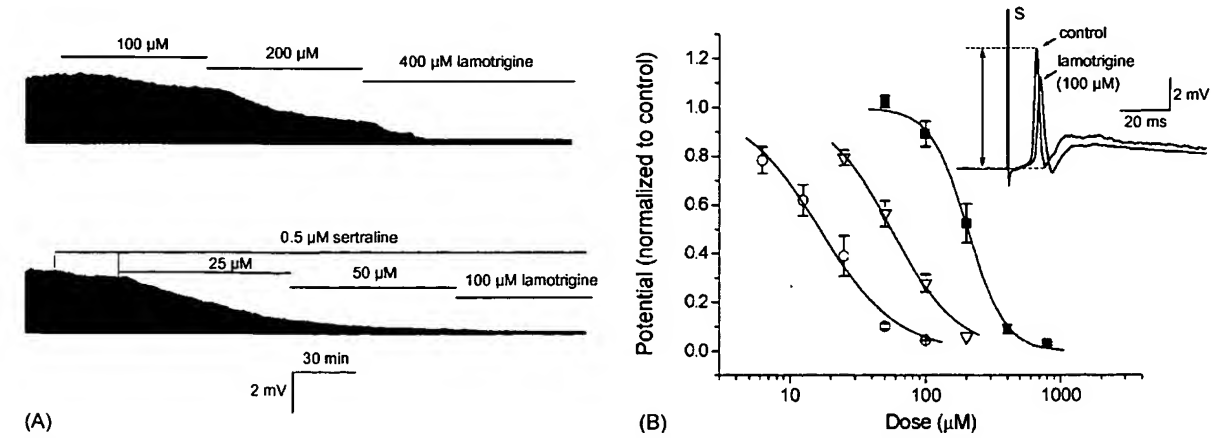

Fig. 1. The effect of sertraline on the reflex inhibitory action of lamotrigine, *in vitro*. (A) Effect of lamotrigine (100, 200 and 400 μM) alone (upper trace) and lamotrigine (25, 50 and 100 μM) in the presence of 0.5 μM sertraline (lower trace) on the monosynaptic reflex (MSR) in two representative experiments. Traces show the amplitude of MSR as a function of time. Lamotrigine caused only moderate inhibition when applied alone at 100 μM, but had much higher effect (75% inhibition at 25 μM) in the presence of sertraline. (B) Dose–response curves of lamotrigine in the presence of 0 μM (■), 0.1 μM (▽) and 0.5 μM (○) sertraline. IC_{50} values are 195.9, 55.7 and 28.9 μM, respectively. Data points represent means ± S.E.M. from 7–10 experiments. The inset shows typical reflex potentials under control conditions and in the presence of lamotrigine. Arrow indicates how MSR amplitude was measured. S: stimulation artifact.

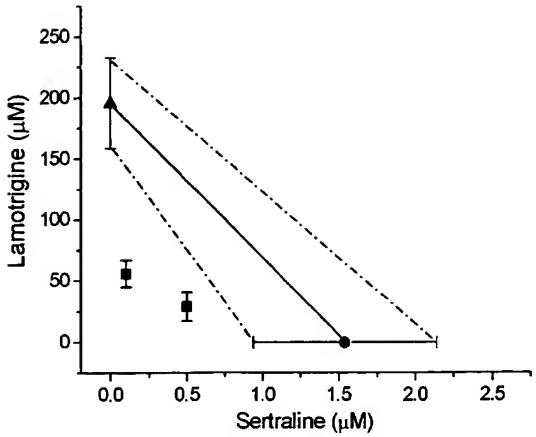

Fig. 2. Isobologram for the interaction between lamotrigine and sertraline to inhibit spinal reflexes, *in vitro*. The IC_{50} value for lamotrigine is plotted on the ordinate (▲) and that for sertraline on the abscissa (●). IC_{50} values were obtained by fitting data to the sigmoid model. The straight line connecting the two plotted IC_{50} values is the isobolographic line, while dashed lines represent 95% confidence intervals. The experimental IC_{50}s of lamotrigine in the presence of sertraline (0.1 and 0.5 μM; ■) are also shown with 95% confidence intervals (vertical bars). If the experimentally determined IC_{50} lies between the dashed lines, then the drug effects would be additive. If the IC_{50} lies below the lower dashed line, it would indicate supra-additive effect. Both points are below the line, and there is no overlapping between the confidence intervals, indicating supra-additive interaction.

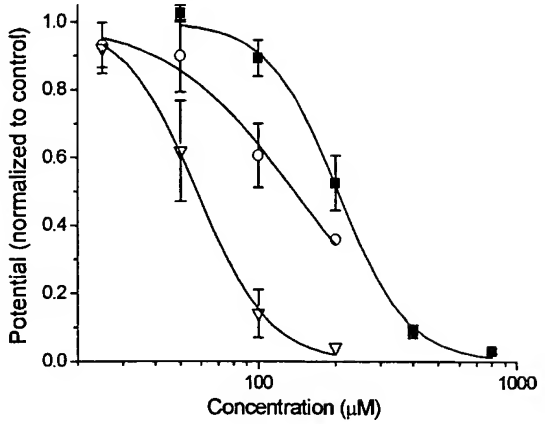

Fig. 4. Effect of the PKC activator PMA on the reflex inhibitory effectiveness of lamotrigine, *in vitro*. Dose–response curves of lamotrigine applied by itself (■) and in the presence of PMA at 0.2 μM (○), and at 0.4 μM (▽). IC_{50} values are 195.9, 138.3 and 60.7 μM, respectively. Data points represent means ± S.E.M. from 4–10 experiments.

receptors with preferential action on the 5-HT_{2C} subtype also decreased the potentiating effect of sertraline, resulting in an IC_{50} value of 90.7 μM for lamotrigine (Fig. 3). On the contrary, the 5-HT_{2C} agonist mCPP (0.1 μM) mimicked the action of sertraline on the inhibitory action of lamotrigine (IC_{50} = 41.6 μM), suggesting a major role of 5-HT_{2C} receptors in the potentiation (Fig. 3).

Furthermore, direct activation of PKC with phorbol-myristil-acetate (PMA; 0.2 and 0.4 μM) resulted in a concentration dependent increase in the efficacy of lamotrigine (IC_{50} = 138.3 and 60.7 μM, respectively; Fig. 4), while blockade of PKC activation by chelerythrine chloride (5 μM) markedly attenuated the potentiating effect of sertraline (IC_{50} = 135.7 μM; Fig. 5). The adenylate cyclase activator forskolin (2 μM) which activates the PKA cascade; failed to alter the reflex inhibitory action of lamotrigine (IC_{50}s: 197.5 and 195.9 μM in the presence and absence of forskolin, respectively). The PKC activator PMA in the presence of sertraline did not increase further the reflex inhibitory effectiveness of lamotrigine (IC_{50} = 56.9 μM; Fig. 3).

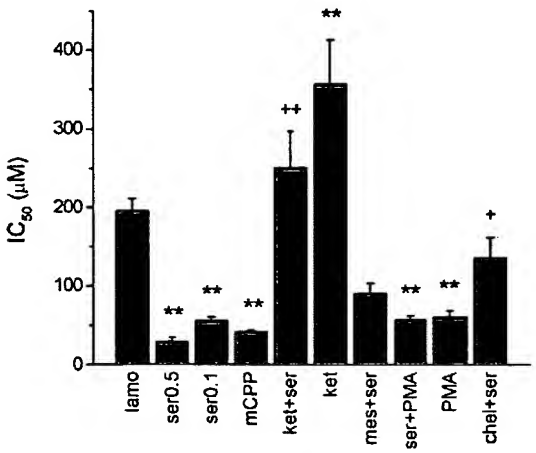

Fig. 3. Effects of various compounds on the reflex inhibitory activity of lamotrigine in the hemisected spinal cord model. The IC_{50} values of lamotrigine, administered by itself (lamo) and in the presence of the serotonin reuptake blocker sertraline (ser0.1, 0.1 μM; ser0.5, 0.5 μM), the 5-HT_{2C} agonist mCPP (0.1 μM), the 5-HT_2 antagonist ketanserin together with sertraline (ket+ser, 1 and 0.5 μM, respectively) and alone (ket, 1 μM), the 5-HT_{2C} antagonist mesulergine together with sertraline (mes+ser, 1 and 0.5 μM, respectively), the PKC activator PMA together with sertraline (ser+PMA, 0.5 and 0.4 μM, respectively), and alone (PMA, 0.4 μM), and the PKC inhibitor chelerytrine together with sertraline (chel+ser, 5 and 0.5 μM, respectively). Columns represent means ± S.E.M. calculated from 4–10 experiments. Asterisks indicate significant differences from lamo ($^{**}P < 0.01$). Plus symbols indicate significant differences from the ser0.5 ($^{+}P < 0.05$; $^{++}P < 0.01$). ANOVA followed by *post hoc* Tukey test.

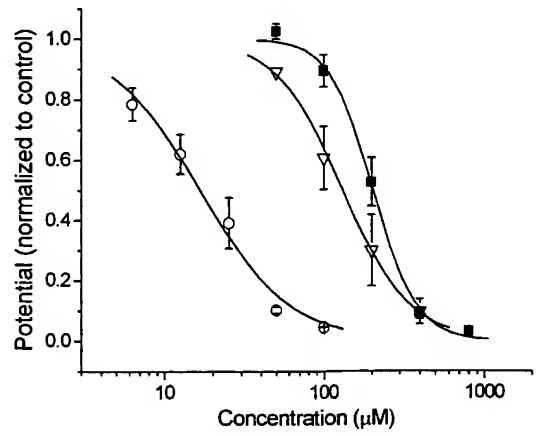

Fig. 5. The potentiating effect of sertraline on the *in vitro* reflex inhibitory activity of lamotrigine, is reversible by the PKC blocker chelerythrine. The reflex inhibitory activity of lamotrigine, administered by itself (■), in the presence of 0.5 μM sertraline (○), and 5 μM chelerythrine + 0.5 μM sertraline (▽). IC_{50} values are 195.9, 28.9 and 135.7 μM, respectively. Data points represent means ± S.E.M. from 4–10 experiments.

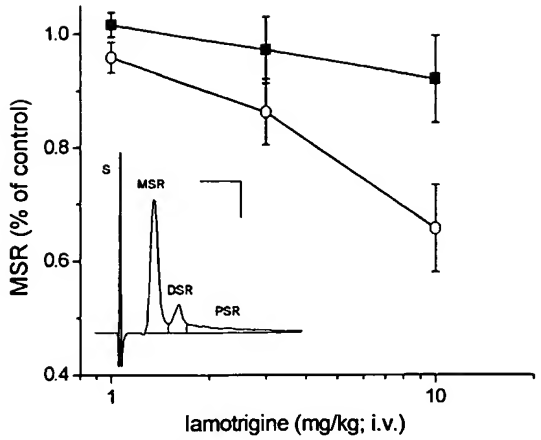

Fig. 6. The effect of sertraline (10 mg/kg, i.v.) pre-treatment on the reflex inhibitory action of lamotrigine, *in vivo*. Effect of lamotrigin alone (■) and after sertraline (○). Data points represent mean ± S.E.M. from 5–12 experiments. Integral of MSR was evaluated. Inset shows the components of a typical ventral root reflex potential evoked by dorsal root stimulation in spinalized rat. MSR: monosynaptic reflex potential; DSR: disynaptic reflex potential; PSR: polysynaptic reflex potential; S: stimulation artifact. Calibration bars: 1 mV and 2 ms.

3.2. Sertraline potentiates spinal reflex inhibitory action of lamotrigine, in vivo

A typical ventral root reflex potential evoked by dorsal root stimulation in spinalized rats consisted of three components. The first, robust peak, the monosynaptic reflex (MSR; 1.5–3 mV amplitude and 1 ms duration), appeared with a peak latency of 1.8–2 ms. MSR was followed by the somewhat more variable disynaptic reflex (0.1–1 mV amplitude and 1 ms duration, about 3 ms latency) and polysynaptic reflex a longer-lasting, gradually declining potential with low amplitude. In the present experiments, drug effects on the under-curve area of MSR were evaluated (Kocsis et al., 2003). Lamotrigine alone had no significant inhibitory effect on MSR up to 10 mg/kg i.v. Pre-treatment (15 min) with sertraline (10 mg/kg; i.v.) increased the reflex inhibitory action of lamotrigine significantly ($p < 0.05$, ANOVA followed by Tukey's test; Fig. 6).

3.3. Fluoxetine potentiates windup inhibitory action of lamotrigine, in vivo

Both lamotrigine and fluoxetine inhibited the windup of wide dynamic range (WDR) sensory neurons dose-dependently, with ED_{50} values of 4.9 ± 0.9 and 1.2 ± 0.2 mg/kg, respectively. The combination of lamotrigine and fluoxetine at a fixed ratio of 5:1 dose-dependently inhibited the windup with ED_{50} values of 1.0 ± 0.5 mg/kg for lamotrigine and 0.2 ± 0.1 mg/kg for fluoxetine. This means an about five-fold increase in the potency of lamotrigine. These ED_{50} values are much lower than the expected ones according to the isobologram (not shown) supposing only additive interaction between the two components.

3.4. SSRIs potentiate antiepileptic activity of lamotrigine, in vivo

Lamotrigine dose-dependently inhibited MES with an ED_{50} value of 2.8 mg/kg. SSRIs administered i.p. (15 min pre-treatment) significantly increased the effect of lamotrigine. The ED_{50} value of lamotrigine decreased to 1.5 and 1.6 mg/kg, respectively when co-administered with fluoxetine (10 mg/kg) or sertraline (10 mg/kg). These doses of SSRIs caused only marginal inhibition (10%) when applied alone in this test (Table 2).

3.5. SSRIs improve side effect profile of lamotrigine

The rotarod test is suitable for characterizing the central side effects of drugs causing impairment in the motor functions and coordination in mice (Dunham and Miya, 1957). The effectiveness of lamotrigine by itself in the rotarod test was 34.3 mg/kg, which was not changed significantly by pre-treatment with sertraline (15 min; 10 mg/kg, i.p.; ED_{50} = 30.8 mg/kg) or fluoxetine (10 mg/kg, i.p.; ED_{50} = 31.1 mg/kg; Table 2). The ED_{50}s of sertraline and fluoxetine in the rotarod test were 120.4 and 45.8 mg/kg, respectively, and the isobolographic analysis suggested no supra-additive synergistic interaction (not shown). In contrast, these doses of the SSRIs caused a marked potentiation in the MES test. ED_{50} of lamotrigine decreased from 2.8 to 1.5 and 1.6 mg/kg, in the presence of fluoxetine and sertraline, respectively. The therapeutic index (TI) calculated from the ED_{50} values in the rotarod test and in the MES test, for lamotrigine alone was 12.2, whereas in combination with fluoxetine (10 mg/kg) or sertraline (10 mg/kg), it increased to 20.7 and 19.9, respectively (Table 2).

3.6. PKC activation potentiates VGSC inhibitory action of lamotrigine

Voltage-gated sodium currents of cultured spinal cord neurons were blocked by lamotrigine in a highly membrane potential dependent way. The $V_{H1/2}$ of the cells were in the range of −50 to −70 mV, therefore the concentration–response relationships were investigated at −60 mV, a membrane potential where approximately half of the channels were in an inactivated state.

Lamotrigine decreased sodium currents of spinal neurons with an IC_{50} value of 19.7 ± 7.9 μM ($n = 5$) at −60 mV. In the presence of the PKC activator, PMA lamotrigine proved to be 10-times more potent (IC_{50} was 1.9 ± 0.7 μM, $n = 5$; Fig. 7).

When the membrane potential dependence of the available current (sodium channel availability) was assessed, PMA (200 nM; $n = 5$), caused a slight shift of the control inactivation curves; thus, $V_{H1/2}$ changed from −56.6 ± 0.8 mV (control) to −61.6 ± 1.7 mV. It caused only slight, non-significant decrease in the maximum available current (13.7 ± 11.9% inhibition) at −130 mV. Lamotrigine (300 μM; $n = 8$) by itself markedly shifted the control inactivation curves towards the more hyperpolarized membrane potentials ($V_{H1/2}$ changed from

Table 2
Effect of selective serotonin reuptake inhibitors (SSRIs) on the anticonvulsant and ataxia-inducing actions of lamotrigine, determined in the maximal electroshock seizure (MES) and rotarod assays, in mice

Treatment		Pre-treatment	Inhibition (%) MES test	ED_{50} (mg/kg) MES test	Inhibition (%) rotarod test	ED_{50} (mg/kg) rotarod test
Lamotrigine (mg/kg i.p.)	0.6	–	0	2.8	–	35.1
	1.25		10		–	
	2.5		20		–	
	5		85		–	
	10		100		–	
	20		–		10	
	24		–		10	
	32		–		30	
	36		–		30	
	40		–		90	
	0.6	Fluoxetine	0	1.5	–	31.1
	1.25	(10 mg/kg i.p.)	60		–	
	2.5		90		–	
	5		100		–	
	20		–		10	
	24		–		30	
	32		–		70	
	36		–		80	
	40		–		70	
	0.6	Sertraline	15	1.6	–	30.8
	1.25	(10 mg/kg i.p.)	35		–	
	2.5		80		–	
	5		90		–	
	20		–		0	
	24		–			
	32		–		70	
	36		–		80	
	40		–		70	
Fluoxetine (mg/kg i.p.)	10	–	0	N.C.	0	45.8
	20		0		–	
	28		20		–	
	40		50		20	
	50		–		70	
	60		50		100	
	80				100	
Sertraline (mg/kg i.p.)	20	–	0	N.C.		120.4
	80		–		0	
	120		–		50	
	160		–		100	
	240		–		80	

-55.1 ± 1.6 to -73.1 ± 1.6 mV), and also decreased the maximum current ($25.7 \pm 5.6\%$ inhibition). The effect of lamotrigine on the steady state inactivation curve did not change in the presence of PMA ($\Delta V_{H1/2}$: -18.0 ± 1.3 and -16.3 ± 1.1 mV). No significant change in the slope of the channel availability curves (k_H) was caused by any of the treatments.

Application of the PKC inhibitor chelerythrine chloride (1 μM; in the intracellular solution) prevented the effect of PMA on the current blocking action of lamotrigine, suggesting that PMA elicited its positive action on the potency of lamotrigine indeed through activation of PKC (Fig. 7).

Together, these results suggest that SSRIs, *in vivo* and *in vitro*, increase reflex inhibitory, anticonvulsant, and analgesic potencies of VGSC blockers mediated by 5-HT_2 receptors *via* PKC activation. Co-application of SSRIs also improved the motor side effect profile of VGSC blockers.

4. Discussion

Participation of the serotonergic system in the modulation of pain- and reflex pathways in the spinal cord is well established (Millan, 1999; Schmidt and Jordan, 2000). Its activation may result in either depression or enhancement of spinal functions depending on what kind of 5-HT receptor subtypes are involved and which neurons are affected (Barnes and Sharp, 1999; Millan, 1999; Schmidt and Jordan, 2000). The application of serotonergic agents thus may produce contrasting or even competing actions (Barnes and Sharp, 1999). In spite of these controversies, the majority of data indicate that 5-HT at the

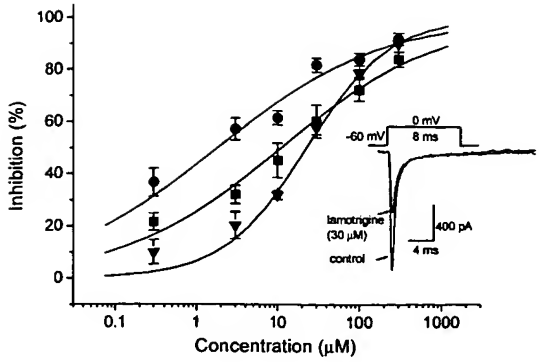

Fig. 7. The synergistic effect of PMA (200 nM) pre-treatment on the sodium current inhibitory action of lamotrigine in cultured spinal cord neurons, and preventive effect of chelerythrine (1 μM) on this potentiation. Effect of lamotrigine alone (■), in the presence of PMA (●), and in the presence of chelerythrine + PMA (▼). IC_{50} values are 19.7, 1.9 and 20.4 μM, respectively. The inset shows a typical sodium current under control conditions and in the presence of lamotrigine (30 μM). Data points represent mean ± S.E.M. from 5–6 experiments.

level of the CNS produces antinociceptive effect (Bardin et al., 2000), and systemic SSRIs and tricyclic antidepressants possess analgesic effect both in experimental animals (Bomholt et al., 2005; McCleane, 2000; Singh et al., 2001) and in humans suffering from chronic pain (Mattia and Coluzzi, 2003; Watson, 1994). The involvement of the different 5-HT receptor subtypes in the mediation of the SSRI's actions on spinal reflex function (Rekling et al., 2000) and pain sensation (Bardin et al., 2000) is not fully understood. Furthermore, a growing body of evidence indicates the role of serotonergic neurotransmission in modifying the excitability of neurons of higher CNS regions as well. In general, depletion of 5-HT results in proconvulsant, while elevation of 5-HT level in anticonvulsant effects, probably through activation of the $5\text{-}HT_{2C}$ receptor subtype (Applegate and Tecott, 1998; Isaac, 2005; Jakus et al., 2003).

Activation of G protein-coupled receptors of different monoamines, such as 5-HT, noradrenaline, or dopamine, can modulate sodium channel functions. This form of regulation implies intracellular signal transduction pathways, like PKA or PKC mediated phosphorylation of sodium channel proteins (Cantrell and Catterall, 2001; Carr et al., 2003). PKC phosphorylates distinct sites of the α subunit of sodium channels, resulting in reduced peak sodium current and altered current inactivation kinetics, as demonstrated in various cells, *e.g.* in *Xenopus oocytes* transfected with Nav1.2a (Schreibmayer et al., 1991; Schreibmayer, 1999), in cortical (Carr et al., 2002) and in hippocampal neurons (Cantrell et al., 1996). In the light of the above findings, it is more understandable how serotonin, acting on the basically excitatory $5\text{-}HT_2$ receptors can mediate an eventually inhibitory effect on sodium channel function. An activation of $5\text{-}HT_2$ receptors and PKC may explain why several SSRI compounds had a depressant action on the parameters measured in our model systems.

Former results of our laboratory (Kocsis et al., 2005) showed that blocking VGSCs of spinal neurons results in a dose-dependent inhibition of reflexes. Our present observations indicate that the anticonvulsant lamotrigine depressed spinal reflexes in the hemisected spinal cord preparation in a qualitatively similar manner to other sodium channel blocking agents used for the treatment of spasticity. The effectiveness of lamotrigine was markedly enhanced by pre-treatment with sertraline. This interaction proved to be clearly supra-additive. Similar potentiating interaction could be demonstrated when combining other VGSC blockers with different SSRI compounds.

The spinal reflex inhibitory effectiveness of lamotrigine could also be enhanced *in vivo* by pre-treatment with sertraline. Furthermore, enhancement of the effect of lamotrigine by fluoxetine was observed in the windup test, which suggests an improved antinociceptive activity. Its anticonvulsant efficacy was also enhanced, in the presence of fluoxetine and sertraline, indicating that the mechanism responsible for the SSRI-VGSC blocker interaction works also *in vivo*. Our findings in the MES experiments are in agreement with those of Leander (1992), who found that fluoxetine enhanced the efficacy of common antiepileptics, such as phenobarbital, carbamazepine and phenytoin, in the MES test. However, further experiments are needed, in adequate models, to prove that a supra-additive interaction between SSRIs and VGSC blockers, similar to that demonstrated at the level of spinal reflexes also exists at higher brain centers involved in seizure initiation and expression. It should be kept in mind that the MES test is mainly suitable for analyzing the motor correlates of seizure associated events. Thus, the idea that the principles revealed in our spinal studies can also be applied to higher brain functions and epilepsy remains to be confirmed in adequate experimental models.

However, no enhanced effect of lamotrigine was observed in the rotarod test following sertraline treatment, *i.e.* the ataxia inducing effect of VGSC blockers may be differentially affected by SSRIs than their spinal reflex inhibitory action. This suggests that sodium channel functions are not uniformly modulated by SSRIs in different brain areas responsible for different brain functions. The observed lack of potentiation has importance regarding the side effect liability (safety margin) of VGSC blocker-SSRI combinations.

Several antidepressants including SSRIs have an anticonvulsant-like, use-dependent blocking action on the sodium channel protein (Lenkey et al., 2006; Nicholson et al., 2002; Pancrazio et al., 1998), the contribution of which to the observed interaction cannot be ruled out. However, ketanserine and chelerythrine reversed the effect of SSRIs in our experiments, furthermore the selective $5\text{-}HT_{2C}$ agonist mCPP and the PKC activator PMA mimicked the action of SSRIs. These findings suggest an indirect action mediated by serotonin transporters, $5\text{-}HT_{2C}$ receptors, and PKC. The effects of mCPP and PMA were somewhat smaller, but did not differ statistically from that of sertraline. Nevertheless, the involvement of other 5-HT receptors and signal transduction mechanisms is conceivable. PMA did not increase further the efficacy of lamotrigine in the presence of sertraline, suggesting a basically common way of action. Compared with ketanserin, the $5\text{-}HT_{2C}$ antagonist mesulergine was less potent to reverse the potentiation caused by sertraline. Its poor potency may be explained by an increasing action on dopaminergic tone (Fuxe

et al., 1985), since D2 receptor stimulation may also lead to PKC activation. Thus, mesulergine may influence spinal reflexes in opposite directions through the dopaminergic and serotonergic systems, which can explain its confusing actions (Yomono et al., 1992).

The fact that ketanserin also reduced the effectiveness of lamotrigine, suggests a tonic modulatory influence of 5-HT *via* 5-HT_2 receptors on VGSCs in the spinal cord.

The exact molecular mechanisms of the modulation of sodium channels by PKC are not fully understood. Neurons express a mixture of sodium channel isoforms and also several PKC isoenzymes, and it is not known which channel is being regulated by which PKC subtype. The role of PKCε in the regulation of Nav1.8, and PKCε and βIIPKC in the regulation of Nav1.7 sodium channels expressed in *X. oocytes* (Vijayaragavan et al., 2004) has been demonstrated. Recent data provide support for the essential role of PKCε in regulation of sodium channels in hippocampal neurons (Chen et al., 2005). However, in other brain areas or in the spinal cord other PKC isoforms might also be involved, and different isoforms of PKC may exert complex and diverse actions.

In addition, PKA may also be involved in this indirect second-messenger dependent regulation of sodium channels, making the above situation even more complex. PKA dependent regulation may require concurrent PKC dependent phosphorylation of distinct phosphorylation sites (Cantrell et al., 2002; Cantrell and Catterall, 2001; Chen et al., 2006). However, in our reflex experiments, activation of PKA by forskolin failed to reproduce the above potentiating effect on the activity of sodium channel blockers (data not shown). Although a partial involvement of PKA cannot be entirely excluded, PKC seems to be essential to the demonstrated potentiating interaction between SSRIs and sodium channel blockers.

An increased efficacy of the VGSC blocker lamotrigine after PKC activation was also demonstrated at the cellular level, in cultured spinal neurons. The effect of PMA to enhance the sodium current blocking effect of lamotrigine was prevented by chelerythrine, confirming the involvement of PKC. The whole complex sequence of events playing roles in the synergism between sertraline and lamotrigine (blockade of the serotonin transporter, 5-HT receptor activation, PKC activation, phosphorylation of specific sites of VGSCs, higher efficacy of VGSC blockers) was not possible to study in this simplified culture system, where no serotonergic innervation was present. However, the system was suitable for studying the process downstream of PKC activation, and the results of our patch clamp studies are in accordance with those obtained in the hemisected spinal cord model.

Although the exact mechanisms underlying the interaction between VGSC blockers and SSRI-s remain to be determined, we think, that the leftward shift in the steady-state inactivation curve elicited by phosphorylation of sodium channel molecules probably contributes to the increased potency of VGSC blockers (Carr et al., 2002). Clinically used compounds preferentially bind to inactivated sodium channels over the resting ones. This could explain their increased effectiveness when a higher percentage of sodium channels are phosphorylated, and accumulated consequently in the inactivated state. Due to their state dependent action they preferentially block overactive sodium channels of neurons involved in pathological processes, and SSRIs seem to make this feature even more prominent. The high degree of potentiation observed with lamotrigine in the hemisected spinal cord model is in agreement with the observation of Kuo and Lu (1997), who found a remarkably high membrane potential dependence of the action of lamotrigine in hippocampal cells. Though the phosphorylation-dependent modulation of sodium channels has been an extensively studied topic recently (Cantrell et al., 2002; Cantrell and Catterall, 2001; Carr et al., 2003), nobody recognized the existence and therapeutical potential of the supra-additive interaction between VGSC blockers and SSRIs based on this regulatory mechanism. Our data demonstrate, that phosphorylation of sodium channels improves the effectiveness of sodium channel blocking agents at least regarding their spinal actions. Since sertraline did not worsen the motor side effects of lamotrigine, the combination of VGSC blockers and SSRIs is expected to result in an improved therapeutic index and improved safety profile compared with those of sodium channel blockers.

Recent data from two small-sized open-label clinical studies, involving 20 patients with spasticity of various origin, and 30 patients with chronic neuropathic pain, indicate that combination treatment with the SSRI sertraline and the VGSC blocker lamotrigine may result in a remarkably effective and safe treatment of both conditions (Molnar and Karpati, 2005a,b). It was formerly reported that co-administration of antiepileptics (sodium channel blockers) and SSRIs results in advantageous features in depression patients (Barbosa et al., 2003; Normann et al., 2002). Our results may provide explanation of these findings. It is conceivable that the recognized advantages of the combination of VGSCs and SSRIs can be utilized in all those therapeutic fields where sodium channel blockers are traditionally used (Clare et al., 2000).

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Study Name	Lamotrigine plus sertraline in neuropathic pain
Design	Open clinical study
Conditions	Neuropathy, peripheral
Population	Patients with chronic polyneuropathic [n = 20] or compression neuropathic [n = 10] pain (n=30)
Treatments	Lamotrigine, 25 [increased to 100] mg/d + Sertraline, 25 mg/d x 8 wks Lamotrigine, 25 [increased to 100] mg/d + Sertraline, 50 mg/d x 8 wks
Biomarker	
Conclusions / Objectives	A combination of lamotrigine plus sertraline was well tolerated and provided good pain relief in patients with chronic neuropathic pain
Intervention Type	Drug therapy
Title	Efficacy and safety of combination of lamotrigine and sertraline in neuropathic pain management Web of Knowledge Record
Reference	Neurology 2005, 64(6, Suppl. 1): Abst P02.159
Authors	Molnar, M.J.; Karpati, G.
Text	The benefits of combining lamotrigine with sertraline hydrochloride were assessed in 30 patients with chronic neuropathic pain. Each patient received a combination of lamotrigine (25 mg/day, increased to 100 mg/day) plus sertraline (25 or 50 mg/day) for up to 8 weeks. At the end of the treatment period, 13 of 20 patients with polyneuropathies and 8 of 10 patients with compression neuropathies showed improvements in their neuropathic pain scores. Overall, the combination regimen decreased pain scores by 25.6% in all neuropathic pain patients. Most common adverse events included diarrhea, slight somnolence and anxiety; no patients experienced severe adverse events during the study.

ASSIGNMENT

WHEREAS Richter Gedeon Nyrt., of H-1103 Budapest, Gyömrői út 19-21, Hungary (hereinafter "Assignor") is the owner by virtue of assignment of the Invention entitled Novel Pharmaceutical Compositions With Increased Activity, described in United States Application No. 10/584,661, filed June 26, 2006; and

WHEREAS Pál Kocsis, of H-1155 Budapest, Mézeskalács tér 5, Hungary; István Tarnawa, of H-1147 Budapest, Kerékgyártó u. 45/C, Hungary; Márta Thán, of H-1148 Budapest, Nagy Lajos Király útja 42-44, Hungary; and Károly Tihanyi, of H-2119 Pécel, Hasznos u. 2, Hungary (hereinafter referred to collectively as "Assignee") is desirous of acquiring the full right, title and interest in and to said Invention for the United States of America, and in and to said United States Application, including reissues and re-examinations;

NOW, THEREFORE, for and in consideration of the sum of One Dollar ($1.00) or equivalent and other good and valuable consideration, the receipt of which is hereby acknowledged by Assignor, Assignor has sold, assigned, transferred and set over, and by these presents hereby sells, assigns, transfers and sets over to Assignee the entire and exclusive right, title and interest in and to said Invention for the United States of America, and in and to said United States Application listed above, including any and all applications that claim the benefit of the patent application listed above, including continuing applications, reissues, extensions, renewals, and reexaminations of the patent application therefore listed above; and in any and all forms of intellectual and industrial property protection derivable form such patent application, and that are derivable for any and all continuing applications, reissues, extensions, renewals and reexaminations of such patent application, including, without limitation, patents, applications, utility models, inventor's certificates, and designs together with the right to file applications therefor; and including the right to claim the same priority rights from any previously filed applications under the International Agreement for the Protection of Industrial Property, or any other international agreement, or the domestic laws of the country in which any such application is filed, as may be applicable; all such rights, title and interest to be held and enjoyed by the above-named Assignee, its successors, legal representatives and assigns to the same extent as all such rights, title and interest would have been held and enjoyed by the Assignor had this assignment and sale not been made. The Commissioner of Patents and Trademarks of the United States of America is hereby authorized to transfer the portion of the title indicated to said application to said Assignee in accordance herewith.

Assignor agrees to execute and deliver to Assignee upon request all lawful documents which may be requested by Assignee.

The undersigned hereby represent that they have full right to convey the entire interest herein assigned, and that they have not executed, and will not execute, any agreement in conflict thereof.

The undersigned hereby grant Paul J. Molino, Esq., Reg. No. 45,350; Deanne M. Mazzochi, Esq., Reg. No. 50,158; Tara M. Raghavan, Esq., Reg. No. 55,557; Dawn Gardner Krosnick, Reg. No. 44,118; and John J. McGuirk, Reg. No. 36,865, all of RAKOCZY MOLINO MAZZOCHI SIWIK LLP, 6 W. Hubbard Street, Suite 500, Chicago, Illinois 60654, power to insert in this assignment any further identification that may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN WITNESS WHEREOF, executed by the undersigned on the date opposite his/her name.

Richter Gedeon Nyrt.

Date: 25 February 2011 By: _____

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